

**Spinal Infections: Analysis of 600 Patients over eleven Years**

*Spinale Infektionen: Analyse von 600 Patienten im Zeitraum von elf Jahren*

**Doctoral thesis for fulfilment of a Doctor Degree in Medicine  
Justus-Liebig-University Giessen**

*Inaugural-Dissertation  
zur Erlangung des Grades eines Doktors der Medizin  
des Fachbereichs Medizin  
der Justus-Liebig-Universität Gießen*

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**Gießen 2018**

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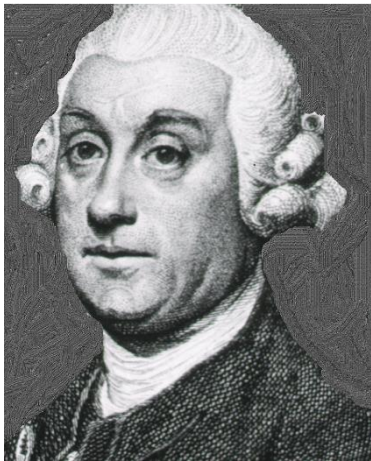
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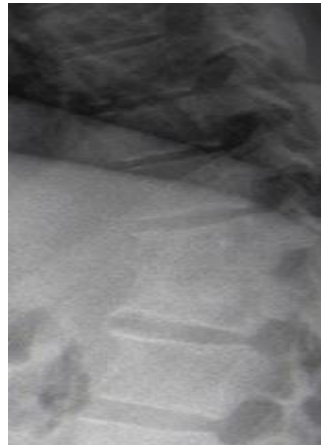
## 1 Introduction

### 1.1 Historical review

The first evidence of spinal tuberculosis (TB) was found in a skeleton from about 5000 B.C and that is older than the written history of spinal infection. Further evidence of spinal infection most likely caused by tuberculosis was found in Egyptian mummies dating from the predynastic time, 3000 B.C. and earlier [1]. **Hippocrates** was the first to describe tuberculosis of the spine. He made distinction between gibbosity above and below the attachment of the diaphragm [2]. The English surgeon **Sir Percivall Pott** (1714-1788) is credited as having recognized the tuberculous nature of this disease in 1779 (**Figure 1**). He published his account of tuberculous paraplegia entitled *Remarks on that kind in palsy of the lower limbs, which is frequently found to accompany a curvature of the spine, and is supposed to be caused by it* (**Figure 2 & Figure 3**) [3].



**Figure 1:** Sir Percivall Pott (1714–1788).



**Figure 2:** Plain x-ray with tuberculous Spondylodiscitis

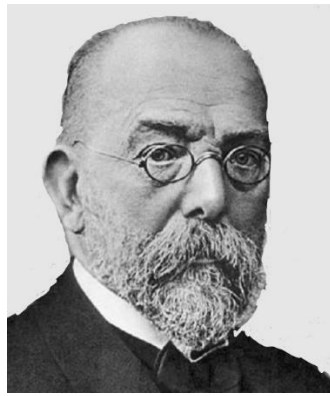


**Figure 3:** CT sagittal view of tuberculous spondylodiscitis

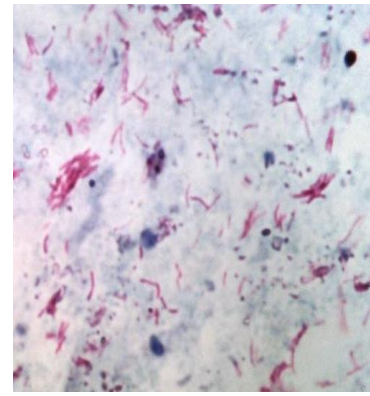
The French physician, **Laennec** (1781-1826), discovered the basic microscopic lesion, the "tubercle", the name by which the disease has been universally known since then (**Figure 4**) [3]. Identification of Mycobacterium as the causative organism by German physician and bacteriologist; **Robert Koch** (1843-1910) in 1882, use of the Bacillus Calmette-Guerin (BCG) vaccination (1945), facilities for radiography examination and management of tuberculosis of the spine were the other significant milestones in the history of tuberculous disease (**Figure 5 & 6**).



**Figure 4:** René Laennec (1781-1826).



**Figure 5:** Heinrich Hermann Robert Koch (1843-1910).



**Figure 6:** The tubercle bacillus, *Mycobacterium tuberculosis* (Ziehl-Neelsen stain)

The first account of pyogenic vertebral osteomyelitis is credited to the French physician **Lannelongue** in 1879 [4]. The first detailed description of these cases was done by **Wilensky** in 1929. He described various cases of acute osteomyelitis, which were caused by staphylococci and streptococci [5]. In 1936, **Kulowski** had published his large series (102 patients) of pyogenic vertebral infections in the English literature [6]. **Compere and Garrison** in 1936 explained and compared the various pathological x-ray changes in inflammatory diseases of the spine [7]. The prognosis of the disease till this time was devastating and lethal. The mortality rate in that period ranged between 40-90% [8-10]. With advancement of diagnostic modalities as well as discovery of the antibiotics, the mortality rate in general has been largely decreased down to 3% [11].

## 1.2 Definitions and basics

Functional spinal unit (FSU) or motion segment is the smallest possible physiological motion unit of the spine to exhibit biomechanical characteristics similar to those of the entire spine. It consists of the intervertebral disc, two vertebrae, and the interconnecting ligaments.

**Epidural abscess** is an infection that forms in the space around the dura and the tissue envelope which surround the spinal cord and nerve roots. **Discitis**, or disc space infection, is an inflammatory lesion of the intervertebral disc. When an infection affects the intervertebral disc and the adjacent endplates, the term to describe this condition is usually

*spondylodiscitis* [12]. If it invades the endplates or the vertebral body, the infection is more correctly named *vertebral osteomyelitis* or *spondylitis* [13]. However, at the time of diagnosis in many cases, the infection has already compromised these two structures; therefore, both terms are frequently used [12].

### **1.3 Anatomical and biomechanical considerations in spinal infections**

#### **1.3.1 Effects of the infectious diseases on the anatomical structures**

The anterior column is affected in 98% of spinal tuberculosis [14]. The richly vascular metaphyseal bone near the anterior longitudinal ligament correlates with the most common site of infections [15]. In the adults, the disc is avascular and the organisms invade the end-arterial arcades in the metaphyseal region adjacent to the disc [16].

In pyogenic spondylitis, the infection spreads either through vessels anastomosing on the periphery of the annulus fibrosus or across the avascular disc by lysosomal destruction of the nucleus pulposus. The disc can be destroyed by bacterial enzymes in a manner similar to destruction of cartilage in septic arthritis [17]. This contrasts to the tuberculous spondylitis, in which the endplates and bone can be extensively destroyed but the disc is frequently preserved due to lack of proteolytic enzymes [18].

With further involvement of the vertebral body, the infection can extend to the epidural space, the subligamentous paravertebral area and contiguous vertebral bodies, i.e. the neural arch and posterior elements. However, in pyogenic infection, involvement of the pedicle, the lamina and the spinous process is uncommon and when this does occur, it should give rise to the suspicion of tuberculous infection [19].

*Griffith and Jones* [20] divided the course of pyogenic spondylitis in three stages in which stability of the spine played a crucial role:

*Initial stage* was within a month of onset. Narrowing of a disc interval and irregularity of endplates were the only signs seen during this period. During this stage, neither instability nor kyphosis was evident.

*Progressive stage* was observed a couple of months after onset. Bone destruction, collapse of softened vertebrae and bone proliferation were observed. Spinal instability followed by kyphotic deformity was apparent over time.



*Healing stage*, evidence of healing, sclerosis and new bone formation were seen from the 8<sup>th</sup> week onwards. During this stage, restabilization might be obtained, although kyphotic deformity may persist.

In pyogenic spondylitis, the lumbar spine is the most commonly affected region followed by the thoracic and the cervical levels [21]. In contrast hereto, in spinal tuberculosis 50% of all the cases occur in the thoracic spine, 40% in the lumbar spine and 10% in the cervical spine [22].

### **1.3.2 Biomechanical features in infectious diseases of the spine**

In pyogenic spondylitis and tuberculosis of the spine, spinal instability and kyphotic deformity can develop due to acute or chronic destructive changes of the spinal column. Both, the location and amount of vertebral body destruction play an important role in the destabilization process in the infected region.

The posterior elements including the facets and laminae get uncommonly affected in cases of infection. Kinematics of the spine is variable at different spinal levels because of anatomical properties, especially the spatial orientation of the facets. This may influence the direction of spinal instability of the infected levels in the initial phase of infectious disease.

In the thoracic region, facet joints lie in a coronal plane, thus restricting the lateral bending but allowing flexion-extension and rotation. Within the thoracic spine, the facet orientation is different; axial rotation is exhibited in the upper levels more than the lower levels. Therefore, axial rotation will be primarily affected in the upper thoracic levels, but in the lower thoracic region, flexion-extension and lateral bending will be compromised.

The facet joints in lumbar region are oriented in the sagittal plane. So, the spinal stability of axial rotation might be initially preserved but flexion-extension and lateral bending will be primarily impaired [23].

In the cervical spine, the facet joints and uncinat processes restrain axial rotation and lateral bending in this region. Thus the spinal instability seems to initiate in the sagittal plane.

*Farfan et al.* [24] experimentally determined the contribution of the facet joints to be 50% in resisting torsional loads. The facet joints do not substantially support axial compressive loads unless the spine is in extension.

## **1.4 Pathophysiology and classifications**

### **1.4.1 Epidemiology**

The spinal column is susceptible to infection, accounting for 2–7 % of all cases of musculoskeletal infections [25]. Estimates of its incidence in developed countries range from 4 to 24 per mill per year. Numerous studies refer to a bimodal distribution with a peak below 20 years and another between 50 and 70 years of age, representing in this group, approximately 3–5 % of all cases of osteomyelitis [13,26]. Furthermore, a 2:1–5:1 male/female ratio has been reported [27,28].

### **1.4.2 Pathogenesis**

#### *1.4.2.1 Routes of spinal infections*

Spinal infections are acquired through the following routes:

- Haematogenous spread
- Direct inoculation-iatrogenic following invasive interventions
- Spread of infection from an adjacent site.

Postoperative infections are increasing in prevalence due to more frequent and more aggressive spinal operations. Depending on the procedure, different anatomic vertebral structures are primarily involved. Microorganisms may be implanted directly into the disc space as the result of diagnostic and therapeutic spinal punctures or during penetrating injuries.

Direct extension of infection from a contiguous source to adjacent vertebra or intervertebral disc is infrequent. Paravertebral pyogenic abscesses usually dissect along tissue planes away from the spine. Continuous (Contiguous) extension is more typical for tuberculous or fungal infections.

#### *1.4.2.2 Risk factors of spinal infections*

Known predisposing risk factors include previous spine surgery, a distant infectious focus, diabetes mellitus, advanced age, intravenous drug use, HIV infection, immunosuppression, oncologic history, renal failure, rheumatological diseases, and liver cirrhosis [29,30,31]. In recent years, an increased incidence has been observed, due to a combined effect between an increase in susceptible populations (particularly history of previous spine surgery) and an improved accuracy in diagnosis [32].

Nowadays, post-procedural discitis represents up to 30 % of all cases of pyogenic spondylodiscitis and has been related to almost all spine surgery techniques [33,34].

It is important to differentiate between systemic and local factors, which can jeopardize the competence of immune system (*Table 1*).

- **Local factors:** include factors that disrupt the integrity of the bone and the soft tissue either through trauma (vertebral fracture) or through iatrogenic procedures (operations). Others such as vascular insufficiency, foreign bodies (Implants), old scars, radiotherapy and instability (lytic olisthesis). The depressed local immunity in these cases is known as *locus minoris resistentiae* [35].
- **Systemic factors:** there are many factors which can negatively affect the immune system; at the *metabolic level* such as DM, obesity, chronic alcohol intake, arterial and venous vascular insufficiency, *iatrogenic* such as cortisone intake, chemotherapy, splenectomy, organ transplantation, primary and secondary immune deficiency diseases, blood diseases and malignancies, systemic infections, drug and nicotine abuse, chronic diseases [36,37].

Systemic factors	Local factors
<ul style="list-style-type: none"> <li>➤ <b>Specific age:</b> elderly and new born,</li> <li>➤ <b>Metabolic diseases:</b> DM, alcohol abuse, obesity, malnourishment</li> <li>➤ <b>General vascular diseases</b> e.g. atherosclerosis</li> <li>➤ <b>Chronic diseases:</b> rheumatic diseases, COPD, liver and renal diseases</li> <li>➤ <b>Immune deficiency:</b> primary or acquired</li> <li>➤ Medication, splenectomy, organ transplantation, long and major surgeries, drug abuse, nicotine abuse</li> <li>➤ Infections</li> <li>➤ Neoplasms</li> <li>➤ Trauma</li> </ul>	<ul style="list-style-type: none"> <li>➤ <b>Disturbances of blood perfusion:</b> venous, arterial or lymphatic insufficiency, neuropathies, nicotine abuse, vasculitis</li> <li>➤ <b>Disintegrity of the bone and soft tissues:</b> operations, scars, trauma, fractures, ulcers, instability, osteosyntheses, foreign bodies, radiotherapy</li> </ul>

**Table 1:** Systemic and local factors affecting the immune system.

#### 1.4.2.3 Microbial Agents

The most common causative agent of infective spondylodiscitis is *Staphylococcus aureus* in all ages, followed distantly by *Staphylococcus epidermis*, gram-negative organisms, anaerobes and others [38]. In infants, the most common isolates are *Staphylococcus aureus*, *Streptococcus agalactiae* and *Escherichia coli*.

Whereas *Staphylococcus aureus*, *Streptococcus pyogenes* and *Haemophilus influenza* are the most common bacterial pathogens in children older than 1 year [39].

Gram-negative bacilli and anaerobes predominate in patients with decubitus ulcers and in immunocompromised patients. Among them, the most important is *E. coli*, which mainly affects elderly men with urinary tract infections. On the other hand, *Pseudomonas* species are associated with epidural infections. Other members of Enterobacteriaceae family, like *Klebsiella pneumonia*, *Enterobacter cloacae* and *Edwardsiella tarda*, have been rarely implicated as the causative agents of spinal infections.

Granulomatous spinal disease is seen with *Brucella* species and is common in endemic areas. *Salmonella* infections are frequently seen in endemic countries like India and Egypt and are associated with sickle cell anaemia. The most common resistant organism that is isolated is methicillin-resistant *Staph. aureus* (MRSA).

Studies have shown that infections caused by resistant organisms may be associated with increased morbidity, mortality and costs. Some risk factors associated with MRSA infections include previous hospitalization, intensive care unit (ICU) stay, indwelling catheters, prolonged antibiotic therapy, advanced age, and exposure to patients colonized or infected with MRSA [40].

*Mycobacterium tuberculosis*, the agent responsible for Pott's disease and skeletal tuberculosis, accounts for 10-20% of all extrapulmonary cases. *Mycobacterium avium-intracellulare* infections may mimic Pott's disease; however, the known association of these agents with human immunodeficiency virus (HIV) is observed for spinal infections as well. Non-tuberculosis mycobacteria, like *mycobacterium xenopi*, *fortuitum* and *kansasii*, also have been rarely associated with spinal infections (*Table 2*).

Conditions	Causative organisms
<b>Pyogenic osteomyelitis</b>	<i>Staph. aureus</i> <i>Streptococcus</i> species <i>E. coli</i> <i>Pseudomonas</i> species <i>Proteus</i> species <i>Salmonella</i> species
<b>Tuberculosis</b>	<i>M. tuberculosis</i> <i>M. avium-intercellulare</i>
<b>Fungal infection</b>	<i>Candida</i> Species <i>Cryptococcus neoformans</i> <i>Aspergillus</i> species
<b>Parasitic infection</b>	<i>Echinococcus granulosus</i> <i>Toxoplasma gondii</i> <i>Taenia solium</i>

**Table 2:** Various causative organisms of spinal infections.

#### 1.4.2.4 Importance of *Staphylococcus aureus* in spinal infections

Humans are a natural reservoir of these bacteria with many people having “normal” colonization in nares, armpits, pharynx and skin. *Staph. aureus* contains adhesion molecules that facilitate its binding to bone matrix. This includes, most notably, the fibronectin-binding protein. In addition, staphylococci can secrete toxins that are capable of bone resorption and have been shown to be internalized by osteoblasts and osteocytes [41].

Bacterial adherence and biofilm formation in implant-associated infection depend largely on the characteristics of implant surfaces and infecting species of microorganisms. *Staphylococcus* species, including *Staph. aureus* and *Staph. epidermidis*, have the ability to produce biofilms on bones and are one of the most important virulence mechanisms by which they cause infections. The biofilm functions as a protective barrier between the bacterial cells and their environment. It facilitates survival under harsh conditions [23].

*Staph. aureus* expresses many potential virulence factors, which can cause rapid spread of infection to the surrounding tissues:

- Invasins that prompt bacterial spread in tissues (kinases, leucocidin, hyaluronidase),
- Surface factors that inhibit phagocytic engulfment (capsule, protein A),
- Biochemical properties that enhance their survival in phagocytes (carotenoids, catalase production),
- Immunological factors (coagulase, protein A),
- Membrane-damaging toxins that lyse eukaryotic cell membranes (haemolysins, leucotoxin, leucocidin),
- Exotoxins that damage host tissues or provoke symptoms of disease,
- Inherent and acquired resistance to antimicrobial agents [42].

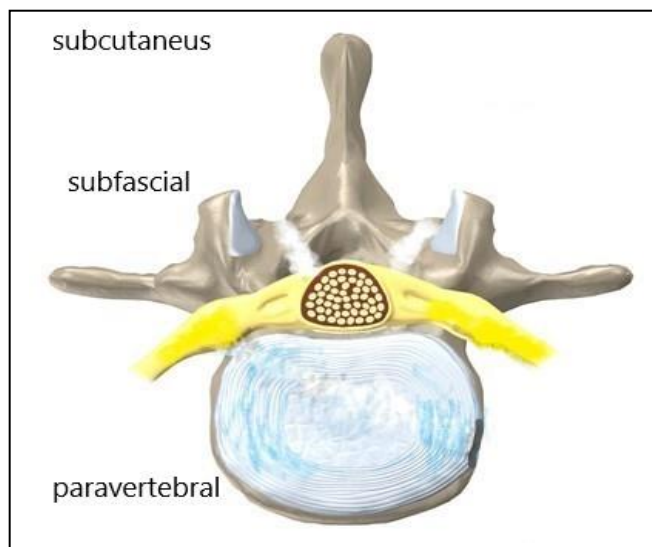
#### 1.4.3 Classification of spinal infections

There are various types of spinal infections depending on the predominant regions of the spine involved by the infection. This includes vertebral osteomyelitis or *Spondylitis* (the involvement of the vertebrae), *Discitis* (an infection of the disc), *Spondylodiscitis (SD)* (an infection of the vertebra and adjacent disc) and *Epidural Abscess* (an infection with pus within the spinal canal). Most often, patients present with only one or two of these clinical entities, but in few severe cases, patients present with all these entities and are considered extremely ill.

### 1.4.3.1 Anatomic classification

**Calderone and Larsen [43]** classified the spinal infections based on the anatomic location of infection including anterior spine, posterior spine and spinal canal as follows (**Figure 7**):

- *Anterior spine:*
  - Vertebral Body:
    - Vertebral osteomyelitis
    - Spondylodiscitis
    - Spondylitis
  - Intervertebral Disc:
    - Discitis
  - Paravertebral Space:
    - Paravertebral abscess
    - Psoas abscess
    - Retropharyngeal abscess
    - Mediastinitis, empyema



**Figure 7:** Anatomic areas of involvement in spinal infections.

- *Posterior spine:*
  - Subcutaneous Space
    - Superficial wound infection
    - Infected seroma
  - Subfascial space:
    - Deep wound infection
    - Paraspinous abscess
  - Posterior elements:
    - Osteomyelitis
    - Deep wound infection
- *Spinal canal:*
  - Epidural space
    - Epidural abscess
  - Meninges
    - Meningitis
  - Subdural space:

- Subdural abscess
- Spinal cord:
  - Intradural abscess

#### *1.4.3.2 Etiological classification*

The most comprehensive classification distinguishes on the etiological causes. It depends on the pathogen responsible for the infection. This may be specific (granulomatous) or non-specific (pyogenic).

#### ➤ Pyogenic-bacterial infections

- Vertebral osteomyelitis
- Discitis
- Spondylodiscitis
- Spinal epidural abscess
- Facet joint arthritis

#### ➤ Granulomatous infections

- Tuberculous infections
- Fungal infections
- Parasitic infections
- Syphilis of the spine

#### ➤ Spinal infections in the immunocompromised patients

They affect the patients with HIV, intravenous drug abuse, long term immunosuppressant therapy and organ transplantation developing spinal infections. The diagnosis is usually delayed secondary to decreased host immunity and lack of obvious signs and symptoms of spinal infection.

### **1.4.4 Forms of pyogenic spinal infections**

#### ➤ **Vertebral osteomyelitis**

Among the spinal regions, the most commonly affected area is the lumbar spine. The infection typically starts in a highly vascular metaphyseal region. It can spread to disc and adjacent vertebral body, frequently destroying the intervertebral disc unlike in TB.

In untreated cases, the vertebral disease progresses to abscess and spreads to the adjacent paravertebral structures or spinal canal [44].

➤ **Discitis**

Here the infection probably begins at the adjacent endplates and the disc is infected secondarily. Gram-positive cocci, especially *Staph. aureus*, are the organisms most commonly isolated from both the blood and from cultures of disc tissues [45].

➤ **Spondylodiscitis (SD)**

SD refers to an infection and inflammation of the base and upper endplates of the vertebrae, as well as the adjoining intervertebral disc. It is the most common complication that occurs in sepsis and post-tonsillectomy, as well as in urinary tract, gastrointestinal and respiratory infections. The main causative organism is *Staph. aureus* (40-60%), even though tuberculosis can be observed in around 20% of the cases. Pyogenic spondylodiscitis can be a complication following surgeries such as laminectomy or disc operations.

➤ **Spinal epidural abscess**

Primary spinal epidural abscess without concomitant vertebral osteomyelitis is uncommon. Haematogenous spread is a common pathogenic mechanism seen in up to 25% of the affected cases with spinal epidural abscess [46]. A large proportion of spinal epidural infections is secondary to iatrogenic causes during invasive spinal procedures. In these infections also *Staph. aureus* is the causative bacteria in about two-thirds of the cases.

➤ **Facet joint arthritis**

Pyogenic facet joint arthritis is uncommon. The most common site is the lumbosacral region. *Staph. aureus* is the most common etiologic microorganism followed by *Streptococcus* species and gram-negative bacteria such as *Pseudomonas aeruginosa*. In a majority of patients, one or more concomitant infectious process, such as arthritis, skin and soft-tissue infections, endocarditis and urinary tract infection (UTI), are found to be due to the same microorganism.



### 1.4.5 Forms of granulomatous spinal infections

#### ➤ Tuberculous infections

The spine is the most common site of skeletal TB and accounts for 50% of the cases. The lower thoracic spine is the most frequently involved region followed by lumbar, cervical and sacral locations.

The primary focus affects the anterosuperior or inferior angle of the vertebral body. The area of infection gradually enlarges and spreads to involve two or more adjacent vertebrae by extension beneath the anterior longitudinal ligament or directly across the intervertebral disc [47].

Five distinct types of spinal column involvement in tuberculous spine have been described radiologically:

- *Paradiscal or metaphyseal type* affecting the two adjacent sides of the disc is the commonest.
- *Central type* with preservation of body height and maintenance of the disc spaces.
- *Anterior periosteal type* eroding anterior surfaces of contiguous vertebral bodies with abscess formation under the anterior longitudinal ligament.
- *Appendicular type* affecting the spinal appendages; pedicles and transverse and spinous processes.
- *Facet joint arthritis* affecting synovial zygapophyseal joints.

In an endemic region, it commonly affects children and young adults. Evidence of other foci and systemic symptoms are often missing. Early symptoms may be back pain or stiffness with initially normal radiological features and diagnosis may be delayed until signs of advanced disease, such as paralysis, deformity or sinus formation develop.

Bacilli are sparse, so smear and culture of pus or tissue are positive only in one-half of the cases. Histologic studies may reveal granuloma with or without caseation in three –fourth of the tuberculous cases.

➤ **Fungal infections**

Fungal infections of the spine are rare and occur mainly as opportunistic infections in immunocompromised patients. They form non-caseating lesions. Fungal infection can occur either through direct extension of a contiguous infection or via haematogenous infection seeding from a distant focus [48].

The common fungal agents causing fungal infections are *Candida* species, *Cryptococcus neoformans* and *Aspergillus* species [48]. Fungal vertebral osteomyelitis caused by endemic fungi, such as *Coccidioides immitis* and *Blastomyces dermatitidis*, has also been described.

➤ **Parasitic infections**

Parasitic infections of the spine are rare. The parasites that have been reported to cause infections of the spine are *Echinococcus granulosus* (Hydatid disease), *Toxoplasma gondii* (Toxoplasmosis) and rarely *Taenia solium* (Cysticercosis).

➤ **Syphilis of the spine**

Syphilis is a bacterial infection caused by the spirochete *Treponema pallidum*. It is primarily a sexually transmitted infection. The final stage is tertiary syphilis and may be further subdivided into three different forms: gummatous syphilis (15%), late neurosyphilis (6.5%), and cardiovascular syphilis (10%) [49]. Syphilis can simulate other granulomatous diseases such as tuberculosis. This makes it very difficult to confirm the diagnosis with histology and imaging. Syphilis can be confirmed by identifying its causative microorganism using dark ground microscopy or serological testing with the latter being the gold standard investigation [50].

**Postoperative spinal wound infection**

It is a devastating complication and can present a number of therapeutic challenges. The infection is most commonly acquired intraoperatively and the source of infection is most likely the environment during the surgery. Despite the development of more effective

prophylactic antibiotics and advancement in implants, techniques and care, the postoperative wound infection is still a growing problem.

*Thalgott [51]* in 1991 categorized the patients according to two parameters, the first being the severity or type of infection, and the second being the host response or physiologic classification of the patient. This classification scheme is based on the clinical staging system for adult osteomyelitis developed by *Cierny [52]*. The severity of infection is classified into the following three groups:

- Group 1: Infection with single organism (superficial or deep)
- Group 2: Deep infection with multiple organisms
- Group 3: Myonecrosis with multiple organisms

The host response, likewise, is classified into the following classes:

- Class A: the host has normal systemic defence, vascularity and metabolism.
- Class B: the host has local and systemic diseases.
- Class C: the host is immunocompromised or severely malnourished.

## 1.5 Diagnostic possibilities

### 1.5.1 Clinical picture

In typical pyogenic spinal infection:

- **Pain** is the outstanding predominant feature in more than 90% of pyogenic spinal infections. The pain is usually subacute during onset. It is generally localized to the spine, exacerbated by movement and may radiate.
- **Febrile illness** and systemic manifestations of infectious toxæmia have been described as occurring in 50% of the cases. Others reported a slight but persistent fever in spinal infections in 65% to 90% of the cases [53,54].
- **Radicular symptoms** are present in 50-93% of cases [55]. Mild neurological deficit, limited to one or two nerve roots, was detected in 28-35% of patients [56,57]. Rarely spinal infections may cause severe deficits such as complete or incomplete paraplegia [25,29]. Neurological deficit (in particular, paralysis) is frequently associated with epidural abscess [58].

- **Paravertebral muscle tenderness** and spasm, and limitation of all spine movements represent the predominant signs, so most patients are bedridden [59].

*Eismont et al.* [60] found that sensory involvement is rare whereas motor and long tract signs are more common because of mainly anterior cord compression. The possibility of serious neurological complication was higher in the thoracic and cervical spine as opposed to the lumbar spine. Therefore, when cephalad levels are involved, more caution should be exercised in assessing possible epidural abscess formation and preventing its neurological sequelae.

The progression of spinal pain to radicular signs followed by weakness and paralysis suggests the formation of an epidural abscess or kyphotic collapse of the infected level [61].

### 1.5.2 Laboratory investigations

The most helpful laboratory investigations are:

- Erythrocyte sedimentation Rate (ESR)
- C- reactive protein (CRP)
- White blood cell count (WBC)

These inflammatory markers are sensitive but non-specific and more helpful in terms of the temporal course rather than as absolute (single) values.

The *white blood cell* count (WBC), often normal, may be elevated in 35-50% of patients. Its elevation is usually moderate and rarely exceeds 12,000 cells/mm<sup>3</sup>. The WBC is not particularly useful in making a diagnosis of spinal infection, but should be part of an infection/fever workup as it may provide some general guidance concerning a response to treatment [62].

An elevation of ESR, although non-specific, is usually seen in almost all cases of spondylodiscitis. The ESR is usually above 40 mm/h on admission with a mean value of 85 mm/hr (normal value 0-20) [29]. Elevation in ESR correlates with the presence of inflammatory response but is not specific for infection. It normalizes in an irregular and slow fashion even after successful treatment of infection. Despite the nonspecific nature of an elevation of ESR, this test provides additional data regarding the possible presence of

infection and some information on response to treatment. With appropriate medical treatment; a progressive decline of the ESR is usually encountered [63].

*C-reactive protein* (CRP) is an acute phase protein synthesized by hepatocytes. Only trace amounts are found in the serum of healthy patients but it increases within 6 hours of the onset of bacterial infection. CRP is elevated in 90% or more of patients with spinal infection and is more specific than ESR. Although CRP and ESR are elevated after spine surgery or infections, CRP normalizes faster than the ESR postoperatively or after appropriate treatment of an infectious process.

**Rosahl et al.** [64] showed that ESR remained markedly elevated ten days after anterior cervical discectomy and fusion with peak on postoperative day three whereas the CRP returned to less than 50% of its peak level by postoperative day five. Therefore an elevation in CRP and/or ESR should not be taken as pathognomonic for an infection; however, these both serve as good screening and surveillance tests in the diagnosis and treatment of spinal infections. **Rath et al.** [65] have reported that the CRP, although non-specific, may be a more clinically useful index than ESR, and should be used to follow the course of the disease.

When leucocytosis, neutrophilia and high values of ESR and CRP are present, they strongly suggest a pyogenic infection. The parameters can reliably be used to monitor treatment response.

**Procalcitonin** (PCT), a precursor of calcitonin produced in the thyroid, is a specific parameter of bacterial infection and elevates significantly during many types of bacterial affection [66]. Since localized infections produce lower PCT levels, clinicians need to use assays with superior functional sensitivities. The PCT has a limited role in the diagnosis of spinal infection, except in cases with strong systemic manifestations of septicaemia.

The determination of antibody titres for putative bacteria is valuable in identifying certain causative organisms. The yield of routine bacteriological and serological tests (positive seroagglutination at titre 1/60) is very high in Brucellosis.

It may be difficult to differentiate between tuberculous and pyogenic infection. A negative Mantoux test indicates non-specific aetiology. A positive Mantoux test is not

pathognomonic for the diagnosis and bacteriological or histological tests should be performed. *Bezaunegui et al.* [67] suggest that even the isolation of mycobacterium tuberculosis in other tissues, fluid samples or histological evidence of caseating granuloma may be sufficient to diagnose haematogenous tuberculous vertebral osteomyelitis. *Nussbaum et al.* [68] reported 21% of cases with tuberculous spondylitis who had no previous or concurrent diagnosis of extraspinal TB, no family history of TB and negative skin test.

Since a multiplicity of microorganisms can be responsible for vertebral osteomyelitis, identification of the causative organism is necessary for appropriate antimicrobial therapy. Up to 24% of the patients may have positive blood cultures. Since these infections are almost always monomicrobial (with exception of those associated with infected pressure sores), it is generally safe to assume that whatever is isolated from blood is also responsible for the bone infection.

Blood, urine and focal suppurative processes should be cultured. In the presence of a septic condition, blood cultures should be obtained, but the hit-rate is low. It can be increased if more than one sample (three to five recommended) is taken from different veins. During a fever spike, a higher percentage of cultures will be positive than during chronic phases of infection. If the cause of septicaemia is known or the blood cultures are positive, patients are less likely to be referred for additional invasive procedures. However, there is a risk that an additional organism may be missed if biopsy is not performed [69].

For those patients with negative blood cultures, however, an attempt to secure a microbiologic diagnosis is imperative, because there are multiple possible causative organisms that require individualized antimicrobial therapy. This is particularly true for intravenous drug abusers, in whom the possibility of isolating gram-negative enteric bacilli is high.

To secure the diagnosis, bone or disc biopsy, or both, is generally required. The specimen should be sent for histological study including special stains for fungi and acid-fast bacilli. Aerobic and anaerobic cultures, fungal and mycobacterial tests should be performed. If brucellosis or fastidious microorganisms are suspected, the incubation periods should be chosen longer (at least 3 weeks).

An attempt should always be made to obtain a direct specimen from the involved vertebral body and/or disc space if an organism cannot be identified by lesser invasive culture

techniques. CT- or fluoroscopy-directed percutaneous needle biopsy can be performed. Needle biopsy under CT guidance is reported to be safe and precise with diagnostic accuracy rate ranging around 70% whereas open biopsies are diagnostic in more than 80% of patients [70]. In a review of spinal infections, *Razak et al.* [71] showed an accuracy of 93.3% in open biopsy techniques. However, the higher sensitivity of open biopsy is mitigated by higher associated morbidity [72].

Non-culture amplification- based DNA analysis is also highly sensitive and specific. It can complement standard microbiologic methods for identifying the cause of infectious spondylodiscitis and contribute to species-specific therapeutic orientation in patients with negative blood and disc aspirate cultures [73].

Whenever possible, antibiotics should be postponed until cultures have been obtained. In addition to bacterial cultures, cultures for fungi and mycobacteria should be obtained in cases where there is a higher suspicion for such infections based on a subacute presentation and a negative gram stain and bacterial cultures.

### **1.5.3 Imaging**

#### *1.5.3.1 Routine radiographs of the spine*

It may take as long as 3-6 weeks after the onset of symptoms for definitive bone destruction to become evident [74]. The first radiographic sign of infection is irregularity of the vertebral endplate of the affected level. As the infection progresses, the erosion of the endplate and the adjacent bone becomes more prominent, leading to narrowing of the disc space, segmental collapse, loss of lordosis and segmental deformity. After a variable period of time, bone regeneration occurs with visible reactive sclerosis as new woven bone replaces necrotic trabeculae (8-12 weeks) [75]. Widening of the paravertebral space due to expansion of the inflammatory process outside the disc causes displacement of the paravertebral line on routine frontal radiographs. Successful treatment will usually produce fusion across the disc space while total vertebral collapse can occur when there is no therapeutic intervention (**Figure 8**).

#### *1.5.3.2 Magnetic resonance image (MRI) scanning*

MRI is considered the gold standard modality in diagnostic imaging for spondylodiscitis [76]. It has a high sensitivity (96 %), specificity (94 %), and provides detailed

anatomical information about surrounding soft tissues and epidural space [77]. The characteristic changes consist of a hypointense signal of the disc and vertebral body on T1-weighted images and a hyperintense signal of the same structures (due to oedema) on T2-weighted images (**Figure 9**). Gadolinium enhancement of the intervertebral disc, vertebral body, and surrounding soft tissues increases the accuracy of MRI, especially when other changes are subtle and also helps in the differentiation of infectious lesions from degenerative (T2 hypointensity favoring Modic endplate changes) and tumour lesions (T1 hypointense relatively to normal bone marrow) [78]. MRI also plays an important role in the distinction between tuberculosis spondylitis and pyogenic spondylodiscitis [79]. Tuberculosis associated spondylitis has an extensive bone destruction pattern with relative sparing of the intervertebral disc, heterogeneous enhancement of the vertebral body and large paravertebral abscesses.



**Figure 8:** Radiographs of the lumbar spine (AP and lateral) showing spondylodiscitis L1/2.

**Figure 9:** MRI (T1 and T2 sequences) of spondylodiscitis L1/2 with epidural abscess Th10-L1.

### 1.5.3.3 Computed tomography (CT)

Advances in CT technology, throughout the last decade, have led to the current generation of multidetector CT scanners that boast faster acquisition, increased anatomical coverage, higher spatial resolution, and isotropic data acquisition. This has resulted in the improvement in diagnostic accuracy and the gain is perhaps best exemplified by the surge in the detailed multiplanar reformations in spine imaging.

Spiral CT imaging with high quality 2D and 3D reformatted images allows a clear assessment of very small vertebral foci of infection, minimal erosions of the end plates, bone



destruction, and soft tissue involvement in the paravertebral and epidural spaces (**Figure 10**). Although, it is not as sensitive as MR imaging, CT remains the preferred imaging modality for the assessment of sequestra and pathological calcifications. Furthermore, it is particularly helpful in identifying atypical foci of tuberculosis especially in the posterior neural arch allowing differentiation from other destructive processes (i.e. metastases, other infections).

Under the guidance of CT, percutaneous diagnostic needle biopsy and percutaneous drainage of abscesses with identification of the causative micro-organism can be done.

Large abscesses could be found in the pre- and paravertebral region, which may extend into the psoas muscle, and along the pleura-lined spaces of the thorax. Paraspinal abscess formation may be better demonstrated on the MRI. The thick nodular rim of an abscess on a precontrast scan represents the hypervascular, hypercellular, fibrotic wall of the inflammatory cavity. After contrast administration, there usually is strong rim enhancement around low attenuation multiloculated fluid collection [80].

The identification of a multilocular and partially calcified paraspinal abscess with a rim enhancement associated to a destructive vertebral body lesion is highly suggestive for a tuberculous rather than pyogenic infection.



**Figure 10:** CT of the lumbar spine (sagittal and axial views) showing spondylodiscitis of Th12/L1 and L3/4 with destruction of the endplates and subcortical osteolysis.

## **1.6 Treatment options**

The goals of management of the patients with vertebral osteomyelitis are:

- To establish a definitive microbiological and histopathological diagnosis
- To eradicate the infection
- To relieve the pain
- To prevent or reverse a neurological deficit
- To establish the spinal stability
- To prevent the recurrence of infection

### **1.6.1 Non-operative treatment**

In early stages, vertebral osteomyelitis usually responds favourably to antibiotic therapy. In the absence of an absolute indication for surgery, when clinical symptoms are mild or bony destruction is minimal, and/or the risks of surgical intervention seem to be very high, a conservative approach may be considered [81]. With the surgical risks in mind, conservative therapy often is the primary option for elderly patients and for patients in poor general condition [82].

While the choice of antibiotics will be largely determined by the culture-sensitivity test, the duration and route of administration of antibiotics is infinitely more controversial in the literature. Author recommendations vary from 6 to 12 weeks [83,84].

Patients need to be closely monitored for adverse drug effects, especially nephrotoxicity (Vancomycin), hepatotoxicity and bone marrow suppression (Linezolid) depending on the choice of antibiotics. The possibilities of therapeutic resistance must be borne in mind when using quinolones, such as ciprofloxacin, for an extended length of time.

Spinal immobilization is a very important aspect of treatment, and often presents a challenge in conservative therapy. Adequate immobilization of the affected segments obviates the need for prolonged bed rest. For the mid-thoracic spine, a reclining brace can suffice. This orthosis holds the affected spine segments in a reclining position, distributing weight to the generally unaffected facet joints, and reducing stress on the diseased vertebrae (*Figure 11*). Even when the thoracolumbar or lumbar region is involved, and the bone destruction is not too severe, immobilization using an orthosis can be enough [13].

However, bed rest for a period of at least six weeks is still required for substantial defects of the anterior column as well as disease affecting the lower lumbar or lumbosacral segments [13,85].

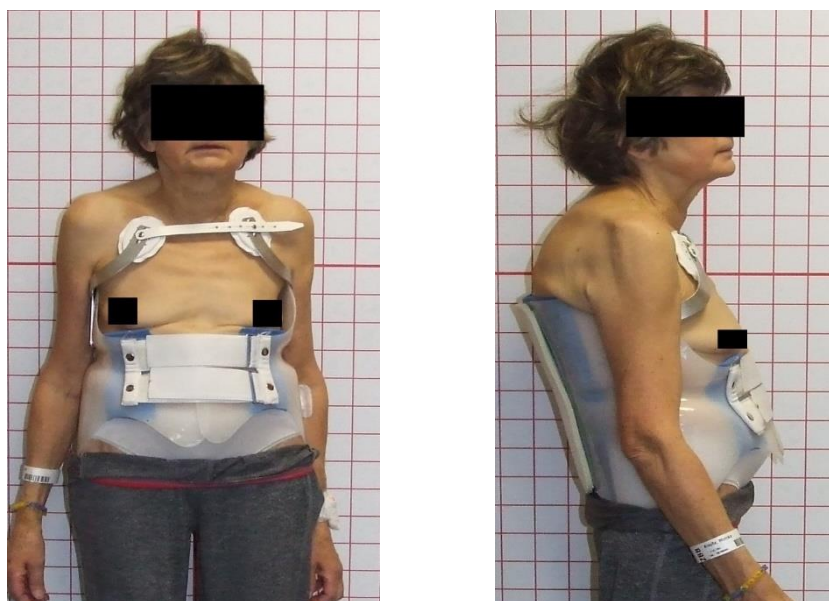
In addition to the risks of bed rest, the rates of pseudarthrosis and instability, which can both ultimately result in kyphotic deformation and chronic pain syndromes, are comparatively high at 16–50% [86].

Conservative therapy should not be continued past four to six weeks if no radiological evidence of reactive bony fusion is present, if the destruction has progressed, or if clinical improvement has not occurred [87].

Within the context of conservative treatment, paravertebral abscess formation requiring decompression can be treated by CT-guided drain insertion and drainage until resorption has been documented by CT-imaging [88].

In elderly patients, the conservative treatment has several limitations such as high incidence of neurological impairment, inability to cooperate and possible occurrence of secondary complications caused by bed rest, such as pneumonia, urinary tract infection and bedsores.

The diminished vascularity of the osteoporotic bone decreases the accessibility of the antibiotics to the infected area and this reduces the healing potential of the bone. The decreased drug clearance in multimorbid patients increases the side effects of administered antibiotics.



**Figure 11:** Thoracolumbar braces which can be used in thoracolumbar infections.

## 1.6.2 Operative treatment

### Indications for surgery in spondylodiscitis

*Urgent surgical intervention* is indicated in patients with [89]:

1. Neurological deficits
2. Sepsis

*Other indications:*

3. Significant bone involvement with instability
4. Impending or current deformities
5. Intraspinous space-occupying processes (i.e. spinal abscess)
6. Unclear aetiology of the process and/or suspected malignant disease
7. Failure to respond to conservative therapy
8. Uncontrollable pain
9. Lack of compliance for conservative measures such as bed rest, orthosis and long-term medications

The goals of surgery are debridement and removal of the septic focus, collection of specimens for microbiological testing and histopathological examination, decompression of the spinal canal, with stabilization and restoration of the infected spine segment, and subsequent bony fusion. In comparison to conservative therapy, this approach allows for a safer and more rapid cure of the infection. Also, mobilization can be begun shortly after surgery [87].

Surgical procedures range from debridement and drainage, decompression to interbody fusion, and grafting with or without instrumentation. The extent of surgery will be determined by the merits of each individualized case.

As spinal infections largely affect the anterior column, the surgical option must be planned to adequately debride the diseased anterior structures. In addition, decompression of the spinal canal is indicated in the presence of an epidural abscess associated with significant neurological deficit.

If either the disease process or the surgical debridement leads to a defect in the anterior column, a tricortical iliac crest bone graft of appropriate length or a cage filled

with graft may be impacted in the defect to restore the anatomy of the anterior column and provide early stability of the segment.

In cases with cervical spinal infections, an anterior approach is recommended with appropriate debridement, decompression and fusion with bone graft, associated with anterior plate stabilization or complemented with posterior instrumentation especially in cases of multilevel and corpectomy cases [90]. Eventually, if the involvement was mainly epidural with no severe destruction of the vertebral body, it is acceptable to proceed toward posterior decompression and fusion [90,91].

In the thoracic spine, the stability is maintained mostly by the rib cage and with physiologically restricted mobility, so that stability issues may not be a significant priority. A purely anterior approach for decompression and fusion (using a transthoracic, posterolateral, or thoracoscopic approaches) is reserved for monosegmental lesions without involvement of posterior elements [92]. Even in this situation, adjunctive posterior stabilization is often considered. In advanced anterior bone destruction and collapse, it is recommendable to combine an anterior approach for debridement, decompression and graft-assisted fusion with additional posterior instrumentation [91,93].

In the presence of an epidural involvement without anterior disc or bony destruction, a posterior approach with decompression is usually the first option.

At the thoracolumbar junction, decompression and stabilization are recommended in the presence of a neurological deficit or extensive epidural invasion. In cases of monosegmental spondylodiscitis with moderate anterior bone involvement and minimal kyphotic deformity, a posterior lumbar interbody fusion may be sufficient [94]. Many surgeons prefer, however, not to invade the posterior tissues with exposure to purulent tissue and would prefer an initial anterior debridement and intersomatic fusion (**Figure 12**) or corpectomy (**Figure 13**) followed by a posterior stabilization procedure.

In the presence of an extensive anterior bone destruction and collapse with segmental kyphosis, a double approach (performed in one or two stages) with anterior debridement and interbody fusion associated with posterior instrumentation results in faster fusion, improved correction of the kyphotic deformity and its maintenance, as well as earlier patient mobilization [59,95]. Classically, bone grafting with tricortical iliac autograft is recognized as

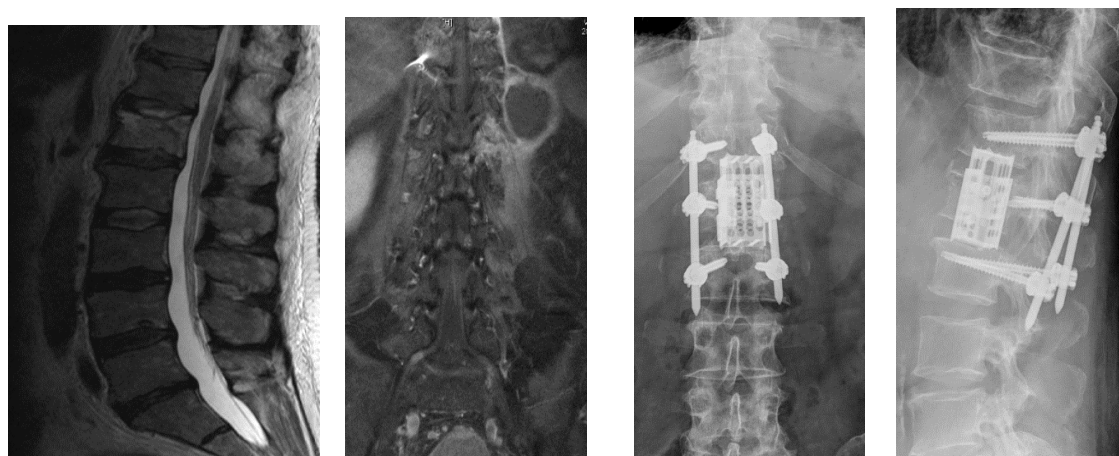
a safe procedure, with excellent and consistent outcomes [96,97]. Structural bone allograft can be used as an alternative, reducing operative time and avoiding donor site morbidity [98].

With the advent and development of minimally invasive spine surgery (MISS), some techniques have been used successfully in the treatment of spinal infection. At the thoracic segments, thoracoscopic approach has been used in some centres with exciting results and additional advantages such as pain reduction and improved postoperative respiratory function, less damage to the soft tissues, resulting in improved outcomes, and shorter hospital stay [92].

In the lumbar segments, posterior percutaneous instrumentation is already regularly used in patients who underwent double approach.



**Figure 12:** MRI and CT sequences of spondylodiscitis Th11/12 (left) and postoperative radiographs (AP and lateral) after anterior thoracoscopic debridement and intersomatic fusion combined with posterior percutaneous transpedicular fixation.



**Figure 13:** MRI sequences of spondylitis L1 with left-sided psoas abscess (left) and postoperative radiographs of the thoracolumbar junction (AP and lateral) after anterior thoracoscopic corpectomy combined with posterior percutaneous transpedicular fixation (right).

## 1.7 Prognosis

With the advent of antibiotics, improved techniques of management, and early recognition, mortality associated with spinal infections has significantly decreased in developed countries and early mortality is generally related to uncontrolled sepsis [99,100]. Despite mortality has declined, the most worrying outcome is the potential for a permanent neurological deficit.

Besides age and spine segment, underlying conditions that are associated with poor prognosis, the major prognostic factor was the presence of a motor deficit before treatment and if the neurological deficits had been present for longer than 36 h [21]. In a series by *Hadjipavlou et al.* [95], 23 % of patients with paralysis on admission recovered completely after surgical decompression.

Despite the presence of neurological deficits on admission, at medium- and long-term follow-up, residual symptoms persist independently of treatment choice and this detrimental outcome is directly related with diagnosis delay [101]. These sequelae are essentially the result of degenerative changes secondary to tissue destruction by the infectious process. *McHenry et al.* [102] reported in a 253 patients follow-up series, 14 % of patients had a recurrence of their infection of which 75 % occurred in the first year after surgery. In childhood, the prognosis is excellent [103,104].

## **2 Aim of the work**

Infections of the spine are still a great problem in many countries. Even in developed countries, the present conditions and trends in infectious disease differ from country to country. The known risk factors of the infectious spinal disease are diabetes, liver cirrhosis, underlying malignant disease, end stage of renal disease, intravenous drug abuse, remote infection and any other immune compromised conditions. The number of patients with spinal infection has been reported to have increased [13,26]. This is probably a result of easier access to better diagnostic methods including MRI, the rising mean age of the patients, increase in the prevalence of multimorbid immunocompromised hosts with chronic debilitating disease.

Over years, the nature of causative organisms, clinical presentation of the patients with spinal infection as well as the radiological and laboratory findings have significantly varied. The most important point for the treatment of spinal infection is the identification of the etiologic microorganism, because long-term antibiotic treatment may be required. The procedures for this step include blood culture, percutaneous tissue biopsy and culture, and open biopsy and culture. However, despite various efforts, in some patients, etiologic organisms cannot be isolated and antibiotics need to be chosen empirically. If the organism cannot be detected, the diagnosis of spinal infection can be based only on the clinical findings, laboratory test and imaging studies. In addition, there is a risk that less experienced doctors differentiate wrongly between pyogenic and mycobacterial spondylitis for patients with a negative bacteriological result.

Germany is one of the most rapidly aging societies in the world with elderly people constituting a large proportion of its population. Given that most advanced countries will be faced with the same situation in the near future, it seems useful to study the demographics, characteristics and microbiological spectrum in those patients in Germany.

The present study included 600 patients with haematogenous spinal infection collected prospectively over a period of eleven years. This gives a possibility to study the change of organism spectrum in a large number of patients with variable comorbidities and various clinical presentations. The collected demographic, clinical, radiological and laboratory data have been analysed and the effect of various causative organisms on these parameters has been studied.



### **3 Patients and methods**

#### **3.1 Study design and material (patients)**

A retrospective analysis of the prospectively-collected data of patients with spinal infection, who were surgically treated in our hospital over a period of eleven years.

Between January 2005 and December 2015, 673 patients with the diagnosis of spinal infections were admitted in the spine department -Zentralklinik Bad Berka- Germany. The data of all patients were collected yielding 600 patients of them (89.2%) with haematogenous spinal infections.

#### ***Inclusion Criteria***

Cases fulfilling the following criteria were enrolled on the basis of clinical, radiological, laboratory, pathologic, and microbiological data:

- Clinical symptoms suggestive of infectious spinal disease: axial pain, fever or chills, radicular pain or numbness, neurological deficit.
- Laboratory abnormalities: C-reactive protein (CRP) >8 mg/dl, white blood cell count (WBC) >11×10<sup>3</sup>/L, erythrocyte sedimentation rate (ESR) >15 mm/h,
- Radiologic abnormalities: spondylodiscitis, spondylitis, discitis, epidural abscess, perispinal abscess and/or pyomyositis on neuroimaging.
- Microbiological results: from blood cultures, intraoperative swabs or biopsies.
- Histopathologic findings: demonstrated non-specific infection or granuloma formation.

#### **Exclusion criteria**

- Patients with postoperative or post-procedural spinal infections,
- Patients who had undergone previous spinal surgery at least at the infected spinal region,
- Patients treated for spinal infections in the period before 2005.

Patients without any positive results from the microbial studies were regarded as cases of pyogenic infection, if they showed characteristic radiologic findings consistent with spinal infection, clinical response to antimicrobial therapy, and their histology not showing granulomatous lesions.

### 3.2 Methods

The patients were identified from admission and discharge coding records, and were cross-referenced with the radiological, microbiological and surgical records.

The following data have been collected and evaluated:

#### 3.2.1 Demographic data

The patients have been grouped according to age, sex and body mass index (BMI). Previous infections, surgeries, antibiotic therapy and its duration have been differentiated. Specific medical diseases such as DM, renal insufficiency, liver diseases and cardiac diseases have been separately described. These diseases can be risk factors for spinal infection or can affect the outcome of the diseases and their treatment methods. All patients have been classified into classes according to ASA- Score (American Society of Anaesthesiologists) (**Table 3**) [105].

ASA –Score	Description
<i>Class I</i>	A normal healthy patient
<i>Class II</i>	A patient with mild systemic disease
<i>Class III</i>	A patient with severe systemic disease
<i>Class IV</i>	A patient with severe systemic disease that is a constant threat to life
<i>Class V</i>	A morbid patient who is not expected to survive without operation
<i>Class VI</i>	A declared brain-dead patient whose organs are being removed for donor purposes

**Table 3:** ASA- scoring system.

#### 3.2.2 Clinical data

We have collected the symptoms at the time of presentation including axial pain (ranged from night pain to mechanical pain), fever, sepsis and weight loss as well the duration of these symptoms (pre-surgical interval; PSI).

The neurological status of all patients has been assessed and graded (grade A to grade E) using the “American Spinal Injury Association” (ASIA) impairment scale. The patient had (grade A through grade D) were considered to have a neurological deficit (**Table 4**) [106]:

ASIA-Grading	Description
<b>Grade A</b> (complete)	No motor or sensory function is preserved in the sacral segments S4-S5
<b>Grade B</b> (incomplete)	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5
<b>Grade C</b> (incomplete)	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
<b>Grade D</b> (incomplete)	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3.
<b>Grade E</b> (normal )	Motor and sensory functions are normal.

**Table 4:** ASIA impairment scale.

### 3.2.3 Radiological data

The following modalities of imaging were used:

- Plain x-rays of the affected region have been done in all patients at the time of presentation,
- MRI of the whole spine with contrast material was done in all patients except in whom the MRI was contraindicated (patients with pacemaker or cardiac defibrillator),
- CT was important for the diagnosis in patients with pacemaker and in patients with cardiac defibrillator. It was also done for further assessment of bone destruction and operative planning.

The following data have been collected:

- Infected levels and infected regions (cervical- thoracic- lumbar- sacral includes cases of sacroiliac joint infection),
- Number of infected segments; included monosegmental (one motion segment) or multisegmental which may be contiguous (continuous) or non-contiguous (with at least one segment not affected in between) which has been described as multifocal infection.

- Type of infection: spondylodiscitis, spondylitis, discitis, epidural abscess or arthritis included sacroiliac joint infection.
- Presence of abscess (epidural, psoas or paravertebral).
- Presence of bone destruction (involvement of the endplates) seen in x-rays and CT of the affected segments.
- Other radiological findings such as instability/lysis, fracture, bone sclerosis, gas formation (vacuum phenomenon), pleural effusion etc.

### **3.2.4 Laboratory data**

#### *3.2.4.1 Inflammatory parameters*

Laboratory parameters were acquired at admission and followed closely. The mentioned values in this study have been measured at the day direct before the surgery done. They included C - Reactive Protein (CRP) measured in mg/dl, Erythrocyte Sedimentation Rate (ESR) measured in mm/hr. The level of CRP and ESR was graded as following (**Table 5**):

<b>Grade</b>	<b>CRP (mg/dl)</b>	<b>ESR (mm/hr)</b>
<b>Normal</b>	≤ 8	≤ 15
<b>Slightly elevated</b>	9-49	16-49
<b>Moderate</b>	50-99	50-99
<b>High</b>	100-199	100-119
<b>Very high</b>	≥200	≥120

*Table 5: Grading of CRP and ESR levels.*

The white blood count, another important inflammatory parameter, was measured ( $\times 10^3/\text{mm}^3$ ) at the time of admission and closely followed. It was also measured at the day before surgery. Its level has been graded as following (**Table 6**):

<b>Grade</b>	<b>WBC (<math>\times 10^3/\text{mm}^3</math>)</b>
<b>Leukopenia</b>	< 4
<b>Normal</b>	4-11
<b>Elevated</b>	11-15
<b>High</b>	15-20
<b>Very high</b>	>20

*Table 6: Grading of white blood cell count (WBC).*

3.2.4.2 Investigations to isolate the causative organism

➤ Blood culture

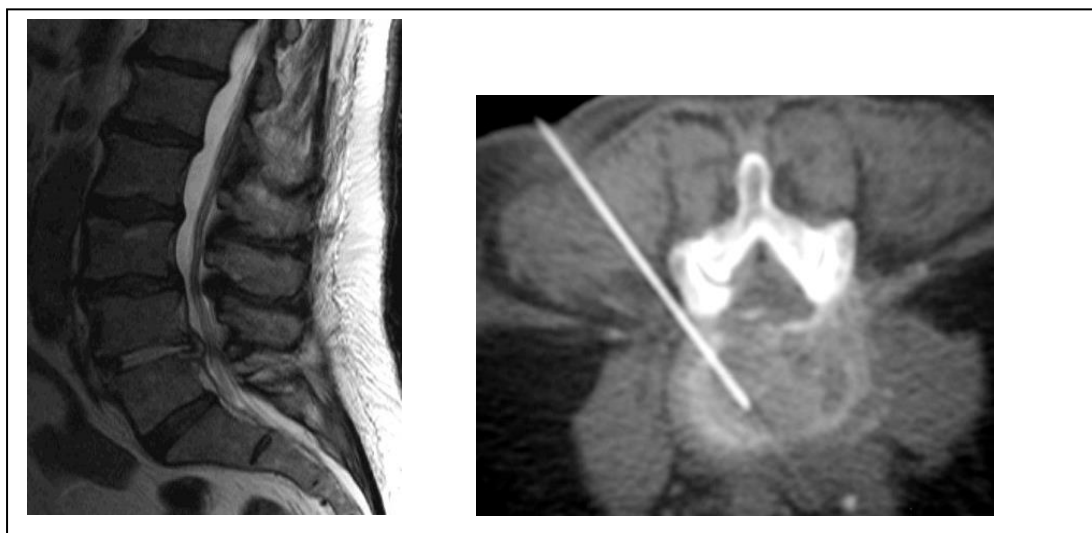
In the patients who had fever or suspected sepsis at the time of presentation, blood was drawn under completely sterile conditions from different venous sites, 20 ml each, for aerobic and anaerobic cultures aiming to start as early as possible with appropriate antibiotic therapy (*Figure 14*).

**Figure 14:** Blood culture bottles (Aerobic and Anaerobic).



➤ Operative biopsy

Material for biopsy was obtained during the definitive operative therapy in 589 patients (98.2%) or rarely, when conservative treatment was regarded, through CT guided biopsy in 11 cases (*Figure 15*).



**Figure 15:** Sagittal MRI showing discitis L4/5 (left) and axial CT fluoroscopic image shows the biopsy needle inserted into the L4/5 disc (right).

The tissues obtained were sent for microbiological examination (culture and sensitivity) aiming to isolate the causative organism(s) and to determine the appropriate antibiotic(s). Histopathological examination of the debridement material to diagnose specific infection (tuberculosis or fungal) and to exclude other possible pathologies such as tumours.

The findings have been compared with those of the corresponding blood cultures and grouped as follows: the same results (same organism in both), negative results (no organism in both) or different results (different organism in both, negative blood culture but positive biopsy or positive blood culture but negative biopsy).

The following data were evaluated:

- Number of organisms isolated: monomicrobial or polymicrobial when more than one organism could be isolated from the site of infection.
- Type of infection: pyogenic, tuberculous, fungal or mixed (superimposed infection) when bacterial infection superimposed a specific one (TB or fungal).
- Type of organism according to: morphology (cocci, bacilli or coccobacilli), gram stain (positive, negative or variable) and growth requirements (obligate aerobes, obligate anaerobes, facultative anaerobic).

Specific organisms, such as Staph. aureus, MRSA, gram negative bacteria, Enterococcus faecalis and Enterococcus faecium, have been mentioned. The association between these organisms and specific medical comorbidities also has been studied.

**(SPSS version 22) program** was used for statistical analyses of the data. T-test was used to compare the continuous variables, and tests and Mann-Whitney test were used to compare the non-parametric variables. The threshold for statistical significance was established at *p-value* <0.005. The whole statistical workup and specific tests have been controlled and proven correctly by Mr. Anter Mohamed Ahmed (Centre for Computer and Statistics- Faculty of Medicine -Asiut University- Egypt).

## 4 Results

### 4.1 Demographic data

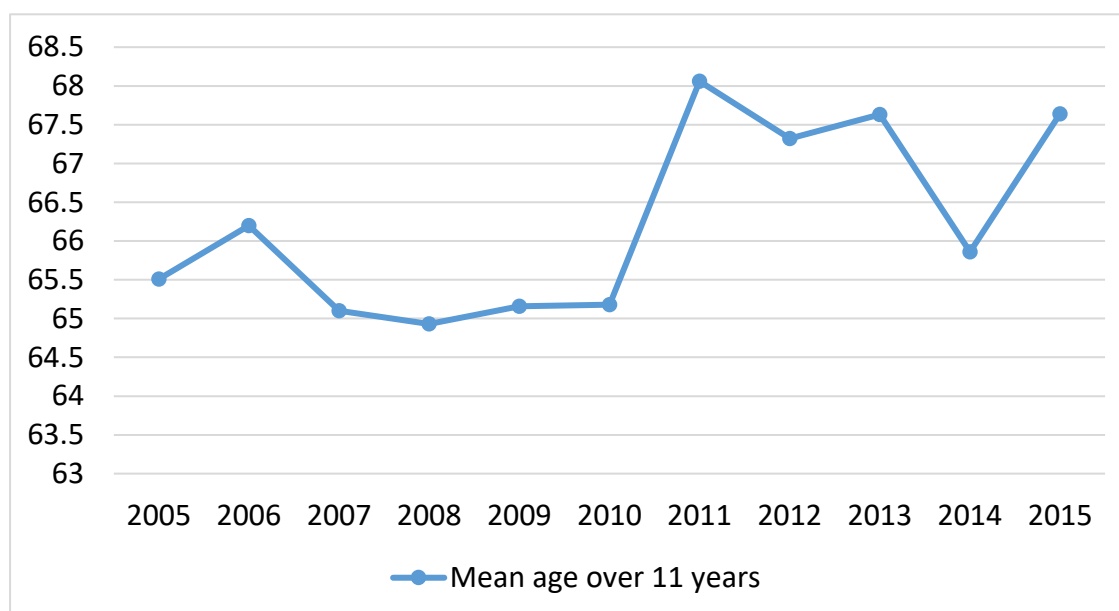
#### 4.1.1 Age and sex

The youngest patient in this study was 4 years and the oldest was 88 with a mean age of 66.1 years. During the period of this study the mean age raised from 65.5 years in 2005 to 67.6 in 2015 (*Figure 16*). The mean age in males was 65.1 years, but reached in females to 67.4 years.

The most affected age group was that between 60-79 years in 381 patients (63.5%). Of a total of 600 patients, 442 patients (73.7%) were older than 60 years (*Table 7*).

Age group (years)	No. of patients	Percentage (%)	No. of males	No. of females
≤20	2	0.3%	1	1
21-39	10	1.7%	7	3
40-59	146	24.3%	90	56
60-79	381	63.5%	223	158
≥80	61	10.2%	29	32
<b>Total</b>	<b>600</b>	<b>100%</b>	<b>350</b>	<b>250</b>

*Table 7: Distribution of the patients according to age groups.*



*Figure 16: Mean age of the patients over a period of eleven years.*

The study included 250 females (41.7%) and 350 males (58.3%). The male gender was more affected than the female (*p-value* 0.000\*); F:M ratio was 1:1.4 (range 1:1 - 1:2.7) over the eleven years. The males were more affected than females in all age groups except in those older than 80 years (M:F=1:1.1).

#### 4.1.2 Body Mass Index (BMI)

In this study, 67.3% of patients were overweight (41.5%) or obese with variable types (25.8%) (*p-value* 0.000\*). Underweight was found only in 7 patients (1.2%). The mean of BMI was 27.54. There was no significant difference in the mean BMI between males and females in this study (*Table 8*).

BMI	No. of patients n=600	Percentage (%)
<b>Underweight</b> (<18)	7	1.2%
<b>Normal weight</b> (18-24.9)	189	31.5%
<b>Overweight</b> (25-29.9)	249	41.5%
<b>Obese</b> ( $\geq 30$ )	155	25.8%
<b>type I</b> (30-34.9)	108	18.0%
<b>type II</b> (35-39.9)	31	5.2%
<b>type III</b> ( $\geq 40$ )	16	2.6%

*Table 8: Distribution of the patients according to BMI at presentation.*

#### 4.1.3 Risk factors and comorbidities

One or more comorbidities were documented in 577 patients (96.2%). Mild diseases were found in 79 patients. The most common comorbidities were cardiac diseases in 289 (48.2%) (Pacemaker in 36 of them), DM in 253 patients (42.2%), renal diseases in 207 (43 patients were on renal dialysis), liver cirrhosis in 34 patients. Immunosuppression by chemotherapy was found in 106 patients and steroid therapy in 74 (because of rheumatoid arthritis in 31 patients of them) (*Table 9*).

In 23 patients (3.8%), no risk factors or comorbidities could be elicited. The mean age in this group was 56.5 $\pm$ 14.4 years (16-80).



<b>Risk Factors</b>	<b>No. of patients n=600</b>	<b>Percentage (%)</b>
<b>DM</b>	253	42.2%
<b>Immunosuppression</b>		
Cortisone	74	12.3%
Chemotherapy	106	17.7%
Neoplasms	112	18.7%
Rheumatoid arthritis	31	5.2%
<b>Renal diseases</b>	207	34.5%
Renal failure; on dialysis	43	7.2%
Chronic insufficiency	164	27.3%
<b>Liver diseases</b>	56	9.7%
Liver cirrhosis	37	5.7%
Hepatitis (A,B,C & toxic)	19	3.2%
Cancer liver	1	
<b>Alcohol abuse</b>	44	7.3%
<b>Nicotine abuse</b>	81	13.5%
<b>Spine fracture (old &amp; recent)</b>	32	5.3%
<b>Lytic olisthesis</b>	11	1.8%
<b>Other site of infection</b>	310	51.7%
Musculoskeletal	158	26.3%
Non- musculoskeletal	213	35.5%
<b>Cardiac diseases</b>	289	48.2%
Pacemaker	36	6.0%
Endocarditis	20	3.3%
<b>Respiratory diseases</b>	187	31.2%
<b>Cerebrovascular stroke</b>	53	8.8%

*Table 9: Distribution of the patients according to risk factors and comorbidities.*

### ➤ ASA- Score

According to ASA-Score, no or mild comorbidities (Class I) were found in 102 patients (17%). 56.7% of the patients were in class III and IV (**Table 10**). ASA-Score had a positive correlation with age (*p-value 0.000\**).

ASA- Score	No. of patients n=600	Percentage =100%
<b>Class I</b>	102	17.0%
<b>Class II</b>	158	26.3%
<b>Class III</b>	237	39.5%
<b>Class IV</b>	103	17.2%

**Table 10:** Distribution of the patients according to ASA-Score system.

### ➤ Other infections (OI)

The presence of OI could be considered as a coincident infection or as a possible primary source of spinal infection. They were found in 310 patients (51.7%).

We have classified OI systematically according to the body system affected and anatomically as follows (**Table 11**);

- Infections below the diaphragm included abdominal, pelvic and lower limb infections,
  - Infections above the diaphragm included chest, upper limbs, head and neck.
- Anatomically, there was no significant correlation between OI and the spinal region infected (cervical, thoracic or lumbar region).

Other infections (Anatomically):	No. of patients n=310	Percentage =51.7%
<b>below diaphragm</b>	187	31.2%
<b>above diaphragm</b>	98	16.3%
<b>Both</b>	25	4.2%
(Systematically):		
<b>Musculoskeletal</b>	159	26.5%
<b>Genitourinary</b>	87	14.5%
<b>Respiratory</b>	84	14.0%
<b>Gastrointestinal</b>	11	1.8%
<b>Cardiovascular</b>	17	2.8%
<b>Multiple systems</b>	58	9.7%

**Table 11:** Distribution of the patients according to presence of other sites of infections (anatomically and systematically).

#### 4.1.4 Pre-surgical interval (PSI)

The time interval between beginning of symptoms and presentation was variable ranging between 5-300 days (mean 41.38 days  $\pm$  33.73).

About 94% of the patients were referred to us from other hospitals or departments. At the time of admission, 59.8% of the whole patients (n=600) had received antibiotics before admission to our hospital (for one day and reaching 250 days in cases of TB).

## 4.2 Clinical findings

The symptoms and signs at the time of admission have been analysed (*Table 12*).

### 4.2.1 Back pain

Axial pain was the most important and most frequent symptom when the patients sought medical advice. It ranged from night pain to mechanical pain and was present in 590 patients (98.3%). The other 10 patients had predominantly septic manifestations.

### 4.2.2 Septic manifestations

In 79 patients (13.2%), septic manifestations were found at the time of presentation; 72 of them (91.1%) were ASA- score class III and IV (*p-value 0.000\**). There was a significant correlation to specific comorbidities such as DM (*p-value 0.001\**), cardiac diseases, renal insufficiency, respiratory diseases, presence of other infections (*p-value 0.000\**) and cerebrovascular stroke (*p-value 0.002\**). The most common organism identified was Staph. aureus in 41 patients (51.9%); 10 of them were methicillin-resistant (*p-value 0.000\**).

Symptom	No. of patients n=600	Percentage =100%
Back pain	590	98.3%
Radicular pain	360	60.0%
Fever	227	37.8%
Sepsis	79	13.2%
Weight loss	13	2.2%
<b>Neurological deficit:</b>	<b>306</b>	<b>51.0%</b>
ASIA A	9	1.5%
ASIA B	2	0.3%
ASIA C	78	13.0%
ASIA D	217	36.2%

*Table 12: Distribution of the patients according to presenting symptoms.*

### 4.2.3 Neurological deficit

In 306 individuals (51%), variable degrees of neurological impairment (ASIA-A to ASIA-D) were found. The incidence of neurological deficit increased with age (*p-value* 0.001\*), amounting to 54.5% in patients older than 60 years (*p-value* 0.003\*) and reaching 57.4% in patients older than 80 years. It had a significant relation to the infected spinal region; being higher in patients with cervical than thoracic or lumbar affection (*p-value* 0.000\*, 0.543 and 0.997 respectively) (*Table 13*).

Parameter	with neurological deficit n=306 (51.0%)	no neurological deficit n=294 (49.0%)	<i>p-value</i>
Mean age (years)	67.7±11.2	64.4±12.4	0.001*
Male: female	1.4:1	1.4:1	0.943
Age groups			0.004*
<60 (158)	65 (41.1%)	93 (58.9%)	
≥60 (442)	241 (54.5%)	201 (45.5%)	
ASA-score III&IV	199 (65.0%)	141 (47.9%)	0.000*
DM	152 (49.7%)	101 (34.4%)	0.000*
Pre-surgical interval (days)	Mean 37.5±30 Median 30	45.4±36.8 35	0.001*
Infected region			
Lumbar n=402	205 (51%)	197 (49.0%)	0.997
Thoracic n=195	103 (52.8%)	92 (47.2%)	0.543
Cervical n=45	35 (77.8%)	10 (22.2%)	0.000*
Preop. conservative treatment			
No. of patients & %	199 (65.0%)	160 (54.4%)	
Duration (days)	17.6±17	19.2±26.7	0.008
CRP (mg/dl)	104±85.1	72.8±73.8	0.000*
ESR (mm/hr)	89.6±36.2	76.7± 36.4	0.000*
WBC ( $\times 10^3/\text{mm}^3$ )	10.8±4.4	9.5±3.9	0.000*
Epidural abscess	190 (62.1%)	122 (41.5%)	0.000*
Multifocal infection	52 (17.0%)	16 (5.4%)	0.000*
Staph. aureus	104 (34.0%)	67 (22.8%)	0.002*
Gram-negative organisms	27 (8.8%)	18 (6.1%)	0.209

*Table 13: Comparison between patients with and without neurological deficits.*

### 4.3 Radiological findings

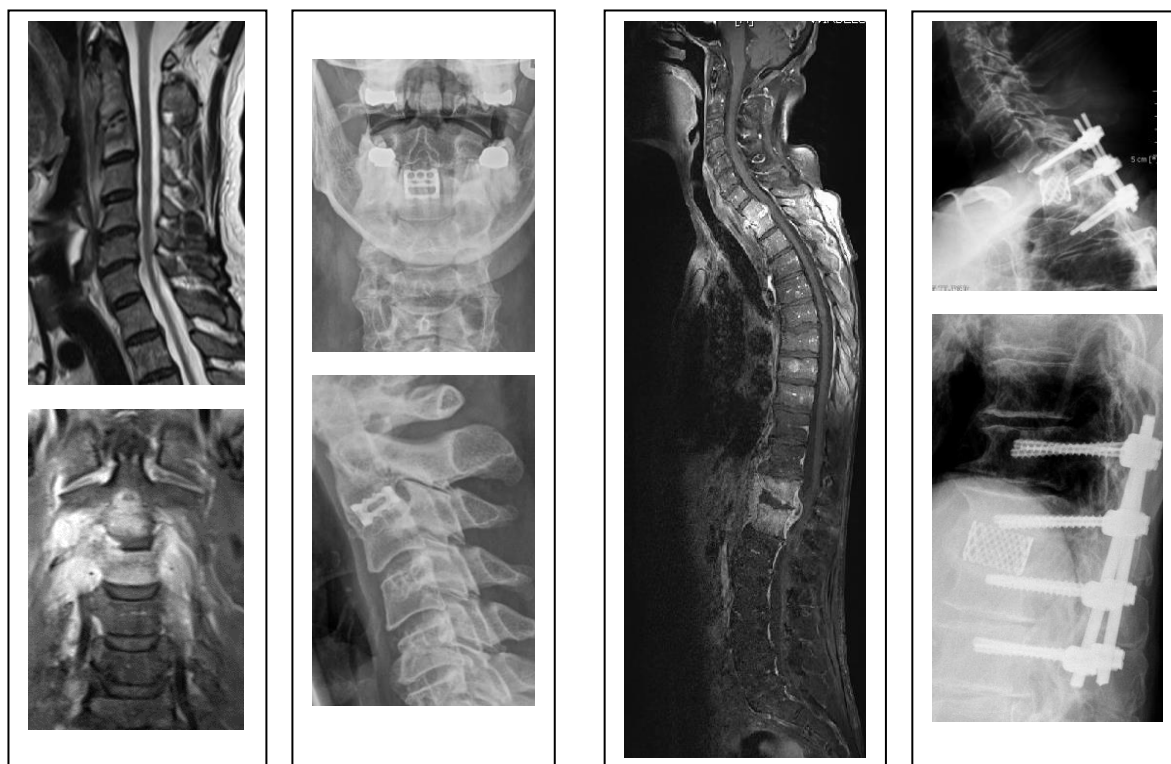
#### 4.3.1 Number of infected segments

In 449 patients (74.8%), one motion segment was infected (*Figure 17*). Infection of two or more segments was detected in 151 patients (25.2%); contiguous infection occurred in 83 individuals (*Table 14*) (*Figure 19*).

#### 4.3.2 Number of infected regions

Unifocal spinal infection with only one region affected, was the commonest form of infestation and apparent in 532 patients (88.7%) (*Figure 20*).

Multifocal (non-contiguous) infection was detected in 68 patients (11.3%) with at least one healthy motion segment in between (*Figure 18*). There was a significant correlation between the incidence of multifocal infection and specific comorbidities such as renal insufficiency in 35 patients (*p-value 0.003\**) and presence of other sites of infection in 47 patients (*p-value 0.003\**). In those patients the incidence of neurological deficits was significantly higher: 52 patients of them had neurological deficit (*p-value 0.000\**). The culture-positivity was specifically higher in those patients, that a causative organism could be isolated in 56 of them (*p-value 0.005\**) (*Table 14*).

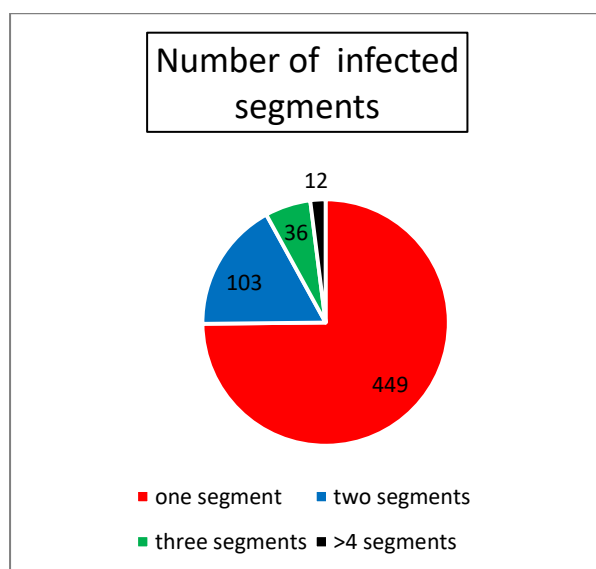


**Figure 17:** MRI sequences of cervical spine with spondylodiscitis C2/3 and postop. Radiographs (AP and lateral views)

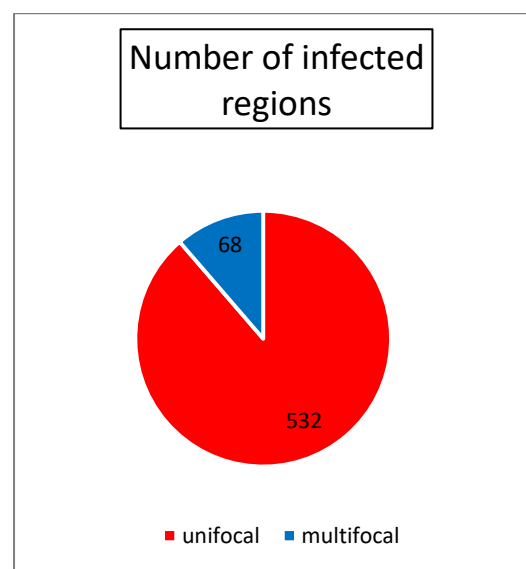
**Figure 18:** MRI sequence of whole spine with spondylodiscitis Th1/2 and Th12/L1 (multifocal) & postop. Radiographs.

No. of infected segments	No. of patients (n=600)	Percentage (%)
<i>one segment</i>	449	74.8%
<i>two segments</i>	103	17.2%
<i>three segments</i>	36	6.0%
<i>≥ four segments</i>	12	2.0%
<b>No. of infected regions</b>		
<i>Unifocal infection</i>	<b>532</b>	<b>88.7%</b>
<i>Non-contiguous infection</i>	<b>(68)</b>	<b>(11.3%)</b>
bifocal	56	9.3%
3 foci	11	1.8%
4 foci	1	0.2%
<b>Infected Regions</b>		
lumbar	402	67.0%
thoracic	195	32.5%
cervical	45	7.5%
sacral	11	1.8%
<b>Junctional zones</b>		
lumbo-sacral	70	11.7%
thoraco-lumbar	139	23.2%
cervico-thoracic	8	1.3%
occipito-cervical	2	0.3%

**Table 14:** Distribution of the patients according to: number of infected segments and spinal regions.



**Figure 19:** Distribution of patients according to number of infected segments.



**Figure 20:** Distribution of patients according to number of infected regions.

### 4.3.3 Other findings

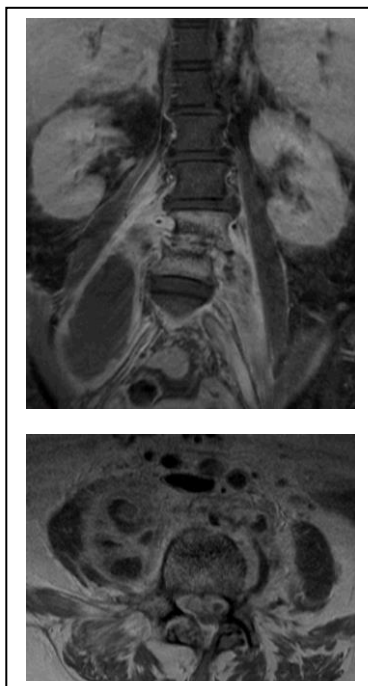
An epidural abscess was found in more than half of the patients (*Figure 21*). It was primary (without vertebral osteomyelitis) only in 14 patients. Of a total of 402 patients, 161 had an abscess in the psoas muscle (40%) (*Figure 22*). In the cases with infection in the thoracic spinal region (195 patients), pleural effusion was diagnosed at the time of presentation in 15 individuals. Spondylodiscitis occurred on top of lytic olisthesis in 18 patients of total of 402 cases who had infection in the lumbar spine (*Figure 23*) (*Table 15*).

Finding	No. of patients n=600	Percentage (%)
<b>Epidural abscess</b>	<b>312</b>	<b>52.0%</b>
Primary	14	2.3%
Secondary	298	49.7%
<b>Psoas abscess</b>	161	26.8%
<b>Lytic olisthesis</b>	18	3%
<b>Infected spinal fracture</b>	32	5.3%
<b>Pleural effusion</b>	15	2.5%

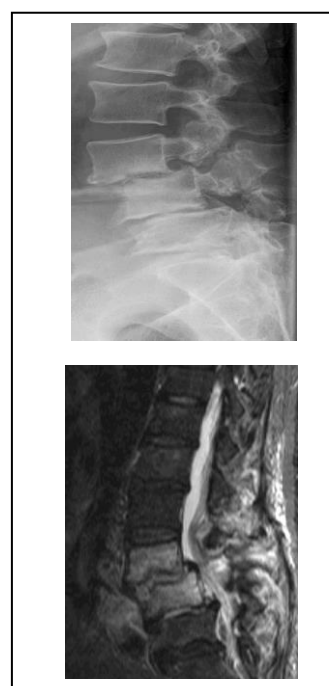
*Table 15: Distribution of patients according to other findings in the neuroimaging.*



*Figure 21:* Spondylodiscitis C5/6 with epidural abscess.



*Figure 22:* Spondylodiscitis L3/4 with psoas abscess.



*Figure 23:* Spondylodiscitis on top of lytic olisthesis L3-5.

## 4.4 Laboratory findings

### 4.4.1 Inflammatory parameters

#### 4.4.1.1 C - reactive protein (CRP)

The mean value of CRP of the whole cohort at the time of admission was elevated to  $88.7 \pm 81.2$  mg/dl (0.8-450). It was  $42.4 \pm 36.2$  (1.7-125.6) in cases of tuberculosis (19 patients) and  $54.6 \pm 24.9$  (21.7-88.8) in cases of fungal infections.

Normal levels of CRP (<8) at admission were found in 54 patients (9%), of them 28 individuals (51.9%) had received antibiotic therapy previously. From this subgroup, 44.1% were scored ASA class III or more. In 18 patients (33.3%) an organism could be isolated. The most common organism identified, while CRP was not elevated, was *Staph. epidermidis* (7 patients).

In 195 patients the CRP was found only **slightly elevated** (9-49 mg/dl), 59.9% of them had received antibiotics before admission. A causative organism could be isolated in 114 individuals (58.5%). *Staph. epidermidis* represented the most common pathogen (22.1%).

**Moderate CRP** (50-99 mg/dl) was found in 151 patients (25.2%). 58.3% of them had received antibiotic therapy before the admission. A causative organism could be identified in 105 patients (69.5%); *Staph. aureus* in 52 (34.4%), *Staph. epidermidis* in 20 (13.2%), followed by *Enterococcus faecalis* in 7 and *E. coli* in 5 patients.

**High CRP** (100-199 mg/dl) was found in 127 patients. A causative organism could be isolated in 103 (81.1%); *Staph. aureus* in 70 patients (55.1%), *Staph. epidermidis* in 10 (7.9%) and *E. coli* in 4 patients. In this group with high CRP epidural abscess was detected in 81 individuals (63.8%).

**Very high CRP** ( $\geq 200$  mg/dl) was found in 73 patients (12.2%). 69.9% of those patients were ASA- Score class III&IV. An organism could be isolated in 65 patients (89.1%); *Staph. aureus* in 50 patients (68.5%), *Staph. epidermidis* in 4, *E. coli* in 3 patients. Epidural abscess was found in 51 patients (69.9%) with a very high level of CRP (**Table 16**).



Level of CRP (mg/dl)	No. of patients n=600	Percentage =100%
Normal ( $\leq 8$ )	54	9.0%
Slightly elevated (9-49)	195	32.5%
Moderate (50-99)	151	25.2%
High (100-199)	127	21.2%
Very high ( $\geq 200$ )	73	12.2%

**Table 16:** Distribution of the patients according to level of CRP.

#### 4.4.1.2 Erythrocyte sedimentation rate

The mean ESR was 83.2 mm/ in the 1<sup>st</sup> hour  $\pm$  36.8 (range 4-140). It was found normal ( $<15$ ) in 19 patients (3.2%) and above 120 in every sixth patient (**Table 17**).

Level of ESR	No. of patients n=600	Percentage =100%
Normal ( $<15$ )	19	3.2%
Slightly elevated (15-49)	96	16.0%
Moderate (50-99)	269	44.8%
High (100-119)	117	19.5%
Very high ( $\geq 120$ )	99	16.5%

**Table 17:** Distribution of the patients according to level of ESR.

#### 4.4.1.3 White blood count

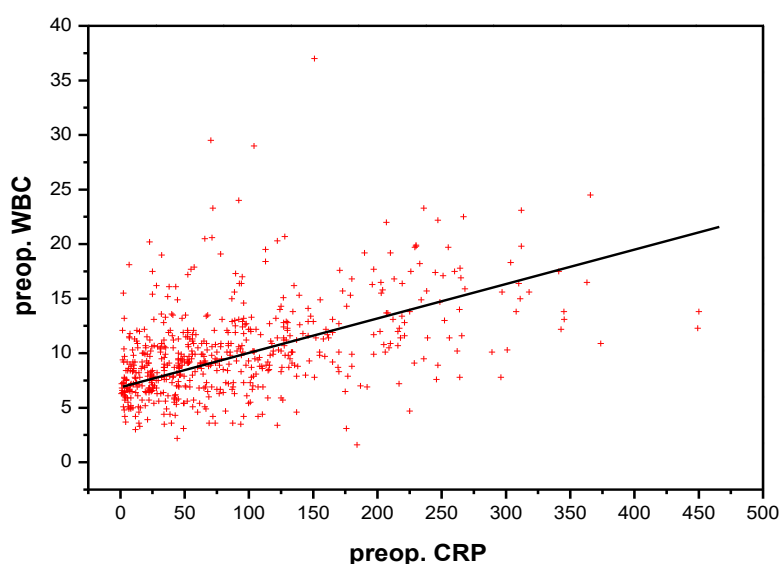
The mean WBC was  $10.1 \times 10^3/\text{mm}^3 \pm 4.2$  ( $1.6-37 \times 10^3/\text{mm}^3$ ). In only in 213 (35.5%) of the patients, it showed pathological values (**Table 18**). Significantly positive correlation was found between the increase of WBC and CRP (*p-value* 0.000\*), *Pearson correlation efficient* was 0.423\*. In only 190 patients (31.7%), there was an increase in both CRP as well as WBC above the mentioned levels. We can say that minimal increase in the level of CRP leads not automatically to an increase in the level of WBC (**Figure 24**).

Normal WBC and CRP was found in 46 patients (7.7%) in spite of the diagnosis of spinal infection. Both parameters were pathological simultaneously in 205 patients (34.2%) (**Table 19**).

The highest levels of inflammatory parameters were found in patients with multifocal spinal infections and the lowest levels in cases with granulomatous infection (TB and fungal) (*Table 20*).

Level of WBC	No. of patients	Percent (%)
<b>Leukopenia (&lt;4)</b>	16	2.7%
<b>Normal (4-11)</b>	387	64.5%
<b>Elevated (11-15)</b>	123	20.5%
<b>High (15-20)</b>	58	9.7%
<b>Very high (<math>\geq 20</math>)</b>	16	2.7%
<b>total</b>	600	100%

*Table 18: Distribution of patients according to the level of WBC.*



*Figure 24: Graphic correlation between CRP and WBC.*

Parameter	Normal WBC	Pathological WBC	Total
<b>Normal CRP</b>	46 (7.7%)	8 (1.3%)	54 (9.0%)
<b>Increased CRP</b>	341 (56.8%)	205 (34.2%)	546 (91.0%)
<b>Total</b>	387 (64.5%)	213 (35.5%)	600 (100%)

*Table 19: Comparison between CRP and WBC in a total of 600 patients.*

Type of infection	CRP	ESR	WBC
<b>Total</b> <b>n=600</b>	<b>88.7±81.2</b>	<b>83.2±36.8</b>	<b>10.1±4.2</b>
<b>Pyogenic</b> <b>n=574</b>	90.7±82.2	84.0±36.8	10.2±4.2
<b>TB</b> <b>n=19</b>	42.4±36.2	67.4±38.3	7.9±2.9
<b>Fungal</b> <b>n=7</b>	54.6±24.9	65.1±15.9	8.3±1.4
<b>Multifocal infection</b> <b>n=68</b>	105.1±89.4	91.8±35.7	10.2±4.6

**Table 20:** The mean values of inflammatory parameters according to the type of infection.

#### 4.4.2 Causative organisms

##### 4.4.2.1 Blood culture

In 228 patients with fever blood culture was obtained and yielded a pathogen in 162 patients of them (71.1%). Of the 66 individuals with no growth in blood culture, in 36 patients an organism could be isolated from the site of infection (**Table 21**). The organisms have been compared to those isolated from the intraoperative biopsies (**Table 22**).

Organism in BC	No. of patients n=228	Percentage (100%)
Staph. aureus	100	43.9%
MRSA	17	7.5%
Staph. epidermidis	14	6.1%
Staph. hominis	1	0.4%
Staph. cohnii	1	0.4%
E. coli	10	4.4%
Pseudomonas aeruginosa	3	1.3%
Streptococcus species	6	2.6%
Acinetobacter (baumanni&calcoactetius)	2	0.9%
Enterococcus faecalis	3	1.3%
Enterococcus faecium	3	1.3%
Moraxella osloensis	1	0.4%
Candida tropicalis	1	0.4%
No growth	66	29.0%

**Table 21:** Distribution of the patients according to the organisms isolated in blood culture.

Organism (blood culture versus biopsy)	No. of patients n=228	Percentage =100%
Same results	106	46.5%
No growth in both	30	13.2%
<b>Different results</b>	<b>(92)</b>	<b>(40.3%)</b>
Different organisms	31	13.6%
Blood culture negative	36	15.8%
Blood culture positive	25	10.9%

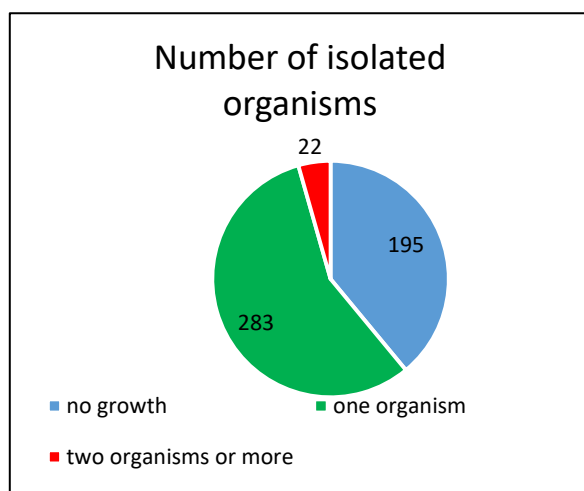
**Table 22:** Comparison between the results in blood culture versus biopsy.

#### 4.4.2.2 Number and type of organisms isolated intraoperatively

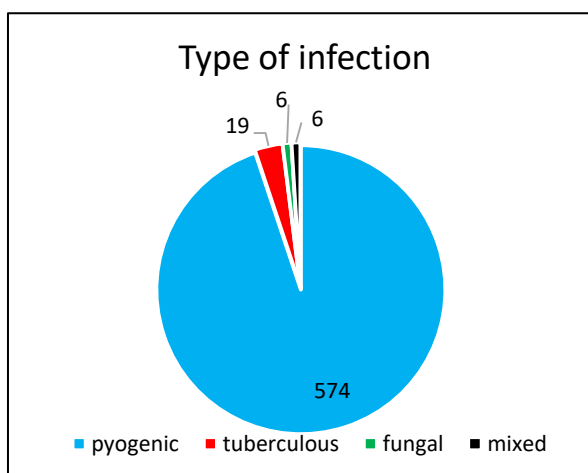
One organism or more could be isolated in 405 patients (67.5%); commonly one pathogen (monomicrobial) was isolated in 383 patients. In 22 individuals, more than one organism has been identified (**Table 23**) (**Figure 25**).

	No. of patients n=600	Percentage =100%
<b>No growth</b>	195	32.5%
<b>One organism</b>	383	63.8%
<b>2 organisms</b>	19	3.2%
<b>3 organisms</b>	2	0.3%
<b>4 organisms</b>	1	0.2%

**Table 23:** Distribution of the patients according to the number of organisms isolated in the biopsy.



**Figure 25:** Distribution of patients according to number of isolated organisms



**Figure 26:** Distribution of patients according to type of infection

Granulomatous (specific) infection was diagnosed in 26 patients, 6 of them were having pyogenic infection on top. The cases with negative culture were diagnosed histopathologically to identify granulomatous infection and they have been diagnosed as pyogenic infection in consideration of clinical, laboratory and radiological findings (*Table 24*) (*Figure 26*).

Type of infection	No. of patients n=600	Percentage 100%
<b>Non-specific</b> (pyogenic)	<b>574</b>	<b>95.7%</b>
<b>Specific</b> (granulomatous)	<b>26</b>	<b>4.3%</b>
<b>Tuberculous</b>	<b>19</b>	<b>3.2%</b>
TB	14	
TB+ pyogenic	5	
<b>Fungal</b>	<b>7</b>	<b>1.2%</b>
Fungal	6	
Fungal+ pyogenic	1	

*Table 24: Distribution of the patients according to the type of infection.*

Staph. aureus was isolated in 201 patients, 30 of them were Methicillin resistant (MRSA) followed by the gram-negative bacteria in 45 individuals (*Table 25*). The isolated organisms are shown in the table below (*Table 26*):

Organisms	No. of patients n=600	Percentage 100%
Staph. aureus	171	28.5%
MRSA	30	5.0%
Staph. epidermidis	90	15.0%
E. coli	20	3.3%
Enterococcus faecalis	15	2.5%
Pseudomonas aeruginosa	11	1.8%
<b>Mycobacterium</b>	<b>9</b>	<b>1.5%</b>
<b>Candida</b>	<b>6</b>	<b>1.0%</b>

*Table 25: Distribution of the patients according to the commonest organism isolated.*

<b>Gram positive bacteria</b>	<b>No. of patients</b>	<b>O2 requirements</b>
<b>Cocci</b>		
<b>1. Staphylococci</b>		
- Staph. aureus	171	facultative anaerobe
- MRSA	30	facultative anaerobe
- Staph. epidermidis	90	facultative anaerobe
- Staph. hominis	1	facultative anaerobe
- Staph. haemolyticus	2	facultative anaerobe
- Staph. intermedius	2	facultative anaerobe
- Staph. lugdunensis	1	facultative anaerobe
- Staph. schleiferi	1	facultative anaerobe
- Staph. warneri	2	facultative anaerobe
- Staph. saprophiticus	1	facultative anaerobe
- Staph. capitis	3	facultative anaerobe
<b>2. Streptococci</b>		
- Strept. bovis	4	facultative anaerobe
- Strept. agalactiae	5	facultative anaerobe
- Strept. dysgalactiae	1	facultative anaerobe
- Strept. pneumoniae	3	facultative anaerobe
- Strept. pyogenes	2	facultative anaerobe
- Strept. sanguis	1	facultative anaerobe
- Strept. salivarius	1	facultative anaerobe
- Granulicatella adiacens	1	facultative anaerobe
- Peptostreptococcus tetradius	1	obligate anaerobe
<b>3. Enterococci</b>		
- Enterococcus faecalis	15	aerotolerant anaerobe
- Enterococcus faecium	8	facultative anaerobe
4. Peptoniphilus asacchrolyticus	1	obligate anaerobe
5. Aerococcus urinae	1	facultative anaerobe
6. Clostridium bifermentans	1	obligate anaerobe
7. Finegoldia magna	1	obligate anaerobe
8. Pediococcus species	1	facultative anaerobe
9. Vagococcus fluvialis	12	obligate aerobe
10. Micrococcus species	1	obligate aerobe
<b>Bacilli</b>		
<b>1. Mycobacterium</b>	<b>10</b>	
- M. tuberculosis	7	obligate aerobe
- M. bovis	2	obligate aerobe
- M. xenopi	1	obligate aerobe
<b>2. Corynebacteriaceae</b>		
- Corynebacterium species	1	facultative anaerobe
- Corynebacterium minussimum	1	facultative anaerobe

- Corynebacterium propinquum	1	facultative anaerobe
- Corynebacterium jeikeium	1	facultative anaerobe
- Corynebacterium pseudogenitalium	1	facultative anaerobe
- Arcanobacterium haemolyticum	1	facultative anaerobe
3. Bacillus sphaericus	1	obligate aerobe
4. Propionibacterium acnes	3	aerotolerant anaerobe
5. Paenibacillus species	1	facultative anaerobe
<b>Gram-negative Bacteria</b>	<b>45</b>	
<b>1. Enterobacteriaceae</b>		
- E. coli	20	facultative anaerobe
- Klebsiella pneumoniae	1	facultative anaerobe
- Klebsiella oxytoca	1	facultative anaerobe
- Proteus mirabilis	3	facultative anaerobe
- Enterobacter cloacae	2	facultative anaerobe
- Proteus vulgaris	1	facultative anaerobe
- Serratia marcescens	1	
- Citrobacter freundii	1	facultative anaerobe
2. Pseudomonas aeruginosa	11	facultative anaerobe
3. Acinetobacter ureae	2	facultative anaerobe
4. Neisseria species	1	facultative anaerobe
5. Bacteroid fragilis	1	obligate anaerobe
<b>Candida</b>	<b>7</b>	
- C. albicans	5	facultative anaerobe
- C. glabrata	1	facultative anaerobe
- C. tropicalis	1	facultative anaerobe

**Table 26:** Distribution of the patients according to the organisms isolated intraoperatively.

The causative organisms have been classified according to the oxygen requirements as following:

- **Facultative anaerobes** (which can grow without oxygen but use oxygen if it is present; make ATP by aerobic respiration if oxygen is present, but are capable of switching to fermentation or anaerobic respiration if oxygen is absent), represented the majority of the organisms.
- **Obligate aerobes** (which cannot make ATP in the absence of oxygen) were found in 24 cases.
- **Aerotolerant anaerobes** (which cannot use oxygen for growth, but tolerate its presence) were isolated in 18 individuals.
- **Obligate anaerobes** (which are harmed and die by the presence of oxygen) were found only in 5 patients.

The most common isolated organism was Staph. aureus (facultative anaerobe), affecting 201 patients (33.5%) (30 of them by MRSA). Tuberculous spinal infection was diagnosed in 19 patients (9 were identified by growth on culture and 10 patients diagnosed histopathologically; in 5 of them non-specific organisms were found on the culture).

**The Staph. aureus** bacterium showed no age predilection (*p-value* 0.074) and frequently occurred in patients who had other sites infections (*p-value* 0.005\*) and/or epidural abscess (*p-value* 0.000\*).

Staph. aureus infected patients presented with sepsis and fever (*p-value* 0.000\*), and had moderate (*p-value* 0.001\*), high or very high (*p-value* 0.000\*) CRP values. The blood culture commonly was positive in Staph. aureus- spondylodiscitis (*p-value* 0.000\*).

**Enterococcus faecalis** has been isolated in 15 patients. Those commonly suffered from renal insufficiency (*p-value* 0.000\*), and presented with sepsis (*p-value* 0.003\*).

**Enterococcus faecium** was found in 8 patients. This infection occurred, like Enterococcus faecalis, commonly in renal patients (*p-value* 0.003\*), but presented with high level of CRP (*p-value* 0.000\*), and increased WBC (*p-value* 0.002\*).

➤ **Polymicrobial vertebral osteomyelitis:**

More than one organism could be isolated from the infection site in 22 patients (3.7%). All of them were older than 50 years, 16 had DM (*p-value* 0.004\*), 17 patients (77.3%) had other sites of infection including bed sores at the time of presentation (*p-value* 0.003\*).

➤ **Gram-negative bacteria:**

Gram-negative bacteria have been isolated in 45 patients (7.5%); 24 males and 21 females with a mean age of 66.96±11.42 years (range 37-83). Neurological deficit was detected in 31 of these patients (68.8%), fever in 20 (from blood culture gram-negative bacteria could be isolated in 8 individuals). E. coli was the commonest isolated organism from the infected region in 20 patients followed by Pseudomonas aeruginosa in 11 individuals. The mean value of CRP was 88.91±72.55, WBC of 10.15±4.9 and ESR 91.09±36.33). The most commonly associated infection was located in the urinary tract (*p-value* 0.000\*). The lumbar spine was affected in 33 patients (73.3%); the lumbosacral junction in 5 cases of them.



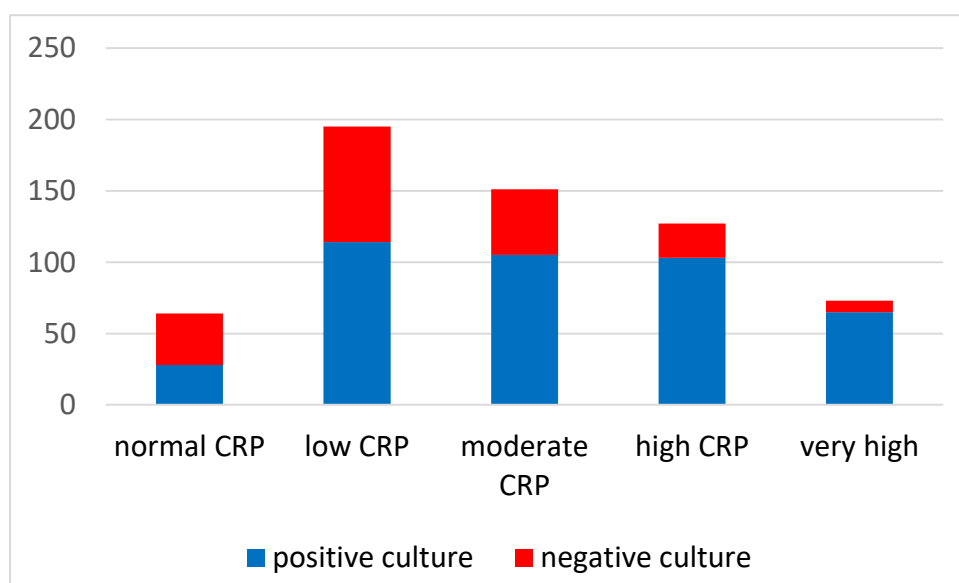
➤ **Negative cultures (no growth)**

In the whole series no organism could be isolated from the site of spinal infection in 195 cases (32.5%), but this percentage decreased to 20.5% by year 2015. In 25 patients of a total of 195, an organism had been isolated by blood culture and antibiotics were being given before the surgery.

Of totally 359 patients who had received antibiotic therapy before the operative procedure (mean period of  $18.3 \pm 21.8$ , range 1- 250), no organism in 108 patients (30.1%) could be isolated (mean period of  $19.4 \pm 16.6$  days 2-90) (*p-value* 0.008). The mean value of CRP in this group was  $55.1 \pm 57.5$ . The probability to isolate an organism was directly proportional to the level of CRP (*p-value* 0.000\*) and significantly related to the period of antibiotic therapy before the operative intervention (*Table 27*) and (*Figure 27*).

Level of CRP	No. of patients n=600	Positive culture	Negative culture
<b>Normal (<math>\leq 8</math>)</b>	54	18 (33.3%)	36 (66.7%)
<b>Slightly elevated (9-49)</b>	195	114 (58.5%)	81 (41.5%)
<b>Moderate (50-99)</b>	151	105 (49.5%)	46 (49.5%)
<b>High (100-199)</b>	127	103 (81.1%)	24 (18.9%)
<b>Very high (<math>\geq 200</math>)</b>	73	65 (89.1%)	8 (10.9%)

*Table 27: Distribution of positive and negative culture in relation to level of CRP*



*Figure 27: Graphic presentation of positive and negative cultures according to the level of CRP.*

Age, sex and the duration of prior antibiotic therapy did not differ between patients with tissue culture-positive and -negative spinal infections, but the inflammatory parameters were significantly higher in the tissue culture-positive patients (104.96 versus 55.1 mg/dl). The most encountered factors associated with positive intraoperative cultures were multifocality of the spinal infection, severity of the comorbidities (ASA-Score III&IV) and fever at the time of presentation (*Table 28*).

Parameter	Positive culture	Negative culture	<i>p-value</i>
<b>No. of patients &amp; percent</b>	405 (67.5%)	195 (32.5%)	
<b>Mean age (years)</b>	65.15±12.4	67.94±10.6	0.029
<b>Male: female</b>	1.5:1	1.4:1	0.943
<b>Age groups</b>			0.029
<60 (158)	118	40	
≥60 (442)	287	155	
<b>ASA-score III&amp;IV</b>	228	112	0.002*
<b>Previous treatment</b>	251	108	0.123
<b>Fever</b>	174	53	0.000*
<b>Abscess formation</b>	388	171	0.000*
<b>Pre-surgical interval</b>	36.86±30.02	50.75±38.77	0.001*
<b>Preop. conservative treatment</b>			
<b>No. of patients</b>	251	108	
<b>Duration (days)</b>	17.82±23.74	19.43±16.60	0.008
<b>CRP</b>	104.96±85.98	55.1±57.51	0.000*
<b>ESR</b>	89.82±34.71	69.6± 37.47	0.000*
<b>WBC</b>	10.64±4.29	9.1±3.85	0.001*
<b>Multifocal infection</b>	56	12	0.005*

*Table 28: Factors affecting the positivity of the tissue cultures*

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## 5 Discussion

Spine infections are caused by three major agents: bacteria, causing pyogenic infections; tuberculosis or fungi, responsible for granulomatous infections; or by parasites, which are a less common aetiology.

In the past, tuberculosis presented the major cause of spinal infections. However, due to the success on diagnosis and treatment of lung tuberculosis, its incidence has decreased during the last 50 years.

In recent years, a raising incidence has been observed, due to a combined effect between an increase in susceptible populations and an improved accuracy in diagnosis [32]. Nowadays, post-procedural discitis represents up to 30 % of all cases of pyogenic spondylodiscitis and has been related to almost all spine surgery techniques [33,34]. The majority of spinal infections are bacterial and monomicrobial [95].

In this study, we have selected the cases of haematogenous spinal infections aiming to study the effect of various causative organisms on the clinical, radiological and the laboratory picture of the patients and well as the relations to various associated comorbidities.

### 5.1 Demographic data

#### Age and sex

In the literature, the age group most affected are individuals in the 6<sup>th</sup> and 7<sup>th</sup> decades [107,108]. The average age in this study was 65.5 years; which is higher than the published results of other studies; (51, 59 and 63 years) [109,21,110]. It was higher in females than males. This difference in the mean age in this study can be explained by the increased life expectancy in the German population; in 2014: 78.15 years for males and 82.86 for females). People older than 65 years in 2013 constituted more than 22% of its population [111]. Thus the occurrence of spinal infection among the elderly is no longer a rare phenomenon.

Males appear to have spinal infections twice as often as females. The reason for this is still unknown [45]. This investigation proved that statement; although the female to male ratio in this study was 1:1.4, which is a little bit higher than that of other studies (e.g. 1:1.23, 1: 1) [21,111]. The ratio was reversed in the age group older than 80 years (M:F=1:1.1) and this could be explained by increased life expectancy in females in comparison to males.

### Associated comorbidities

The most commonly described comorbidities are increased age, immunosuppression, steroid medication, drug abuse, DM and previous spine surgery [10,57,59]. In this study, more than 96.2% of patients had comorbidities, 56.7% had ASA-scoring class III and IV with positive correlation with age (*p-value* 0.000\*). This can be explained by the higher age of patients in this cohort (65.5 years), which is the age of immunocompromise and vulnerability to spinal infections [112].

Increased BMI is considered a risk factor for development of surgical site infections [113]. In this study of cases with haematogenous spinal infection, more than 2/3 of the patients were overweight and obese. Reasons could be a true comorbidity or consequence of limited mobility of those patients with other medical diseases.

Weight loss is known as a general clinical finding in patients with infections. In this study, BMI < 18 (underweight) was found only in 7 patients; 5 of them rated ASA-class II, 3 had hyperthyroidism and 3 individuals had GIT diseases. Specific infection, Tuberculosis “the consuming disease” occurred only in two of the underweight patients. Thus weight loss seems to have no relation to spinal infections of our time.

The presence of other sites of infection could be considered as a coincidental infection or as a possible primary source of spinal infection (51.7%). Since there was no significant correlation between an anatomical location and the infected spinal region, systemic bacteraemia seems to be the cause of spinal infection rather than spread through venous dissemination. Also, the presence of other sites of infection increases the incidence of multifocal spinal infection (*p-value* 0.003\*) and the success to isolate an organism from the infected region.

Infection of the musculoskeletal system was found in more than half of those patients with other sites of infection (310 patients). In this study, Staph. aureus was the commonest organism that could be isolated (*p-value* 0.005\*).

Systemic immunity of the elderly patients could be suppressed by various medical diseases. Suppression of the local immunity is also described and known as *locus minoris resistentiae*, which is defined as a site of less resistance, any part or organ which is more

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susceptible than others to the attack of a morbid agent. The sites of trauma or instability may lower the local immunity and these support the theory of *locus minoris resistentiae*.

### **Pre-surgical interval (PSI)**

The time interval between the beginning of symptoms and presentation for surgery was variable, ranging from 5 to 300 days (mean 41.38 days  $\pm$  33.73). Longer PSI means failure of conservative treatment or late diagnosis. Misdiagnosis is not uncommon especially in elderly patients due to the prevalence of degenerative changes of the spine. In this context, a significant positive correlation (*p-value* 0.011\*) has been found between the longer PSI and existence of bone destruction. Presence of osteoporosis and reduced vascularity of bone in this age as well as abscess walls can jeopardize the accessibility of antibiotics to the infected area and reduce the healing potential of the bone.

## **5.2 Clinical findings**

**Back pain** is the commonest non-specific symptom in nearly all spinal diseases. It is highly significant, if associated with fever or neurological deterioration. However, it is not diagnostic for spinal infection, but it is a good clinical parameter for follow-up.

**Fever** is typically not present in haematogenous spinal infections and accounts for less than 20% of patients, however reached 38% (228 patients) in this study. Blood culture was taken in these patients with fever and revealed positive culture in 162 patients (71.1%). The success to isolate an organism from the site of infection in those patients rated at 76.32% (174 individuals).

**Septic manifestations** were mostly found in polymorbid patients with ASA score III and IV (*p-value* 0.000\*). Those patients have suppressed immunity and presented with severe symptoms more than the others with class I and II.

**Neurological deficit** is the alarm for presence of a compressing intraspinal element, commonly an epidural abscess (*p-value* 0.000\*). Rapid diagnosis and intervention is mandatory.

These infections in elderly patients are characterized by a high incidence of neurological deficit, which reached up to 58% in patients older than 65 years.

In this study, more than half of the patients had some degree of neurological affection, which significantly increased with age of patients (*p-value 0.001\**) irrespective to presence of a compressing element. This aspect should be considered regarding the choice of the treatment method.

The neurological involvement varied according to the spinal region affected. The cervical and thoracic spinal regions have a special vascular and anatomical relation to important neurological structures, so that the spondylodiscitis in this region is more associated with neurological deficits and morbidities [114,115]. It occurred in 77.8% of the cervical (*p-value 0.000\**), 52.8% of the thoracic and in 51% of the lumbar spinal infections. This could also be due to the variability of space available to the neural tissue.

### 5.3 Imaging findings

With increased age of the patient degenerative changes and age related changes in the sagittal profile could be seen in the imaging studies, so that additional changes caused by infection are not so apparent in the early stage of the infectious disease. Therefore, a high index of suspicion must be maintained [77]. These radiological changes (bone destruction) are proportionally related to the PSI as well as the aggressiveness of the infection.

Sensitivity, specificity, and accuracy of MRI are reported as 96%, 92%, and 94%, respectively. Associated oedema typically is pronounced and affects much of the vertebral body and inter-vertebral disc [70].

CT was valuable for the diagnosis when MRI was contraindicated (36 patients with pacemaker) as well as for further assessment of bone destruction and operative planning. In the recent years due to advanced devices and better availability of experienced rhythmologists, the number of absolutely contraindicated MRI- investigations dwindled in our series since there is the option to switch off the pacemaker temporarily.

The level of spinal involvement varies and infections have been recorded at all levels of the spine [116]. The most common site of pyogenic spinal infection is the lumbar spine (45–50%), followed by the thoracic (35%), cervical (3–20%), and sacral region [117]. In our patients, lumbar was the most affected spinal region with 67%, followed by thoracic and with 7.5% least in the cervical area. This distribution was in the same range as in various studies in the literature [57,98,118].

Pyogenic spondylitis typically involves two adjacent vertebrae and the intervening disc [61]. Unifocal spondylodiscitis was the commonest form reported; 90.1% and 98.4% [29,118]. **Renker** [119] described an incidence of multifocal spinal infection occurring in 11%. In a study of 1138 consecutive cases of spinal infection, 77 patients were affected at non-contiguous levels (6.8%), which was described as metastatic spinal infection [120]. In this study, one segment was affected in 449 patients (74.8%). Contiguous (= continuous) spinal infection is a more aggressive form with two or more adjacent segments affected (83 patients). The non-contiguous (multifocal) spinal infection denotes a systemic infection with non-adjacent segments affected with at least one normal disc space in between. This occurred in 68 of our patients (11.3%). The level for which the patient had been presented was denominated as the primary.

The multifocal form represents a systematic dissemination of infection in the immunocompromised patients especially those with other sites of infection (*p-value* 0.003\*). In these cases, the incidence of neurological impairment was significantly high (*p-value* 0.000\*) and the inflammatory parameters reached high levels.

MRI of the whole spine was the standard imaging method in all cases of spinal infection and allowed to detect the multifocal form of the disease. In patients with neurological deficits, emergent MRI imaging is mandatory to exclude presence of an epidural abscess.

The diagnosis of pleural effusion, psoas abscess, spondylitis of a fractured vertebra or infected lytic olisthesis may be important to determine the side to be approached as well as the surgical technique.

## 5.4 Laboratory findings

### 5.4.1 Inflammatory parameters

The inflammatory parameters including ESR, CRP and WBC can give an evidence of spinal infection, however they are nonspecific markers of infection [13].

- **ESR** is a sensitive laboratory indicator of pyogenic infection, which is positive in more than 90% of patients with spinal infections (positive in 96.8% in this study). It ranges in patients with pyogenic spondylitis from 43–87 mm per hour [29]

(range 4-140 in this study). Increase in sedimentation rate correlates with the presence of inflammatory response but it is not specific for infection.

- **CRP** raises within six hours of the onset of a bacterial infection. It is elevated to variable degrees in 90% or more of patients with spinal infection [121]. It reached 91% in our cohort study.

Therefore an elevation in CRP and/or ESR should not be taken as pathognomonic for an infection; however, these both serve as good screening and surveillance tests in the diagnosis and treatment of spinal infections.

- **WBC:** Leucocytosis is not described as an obligatory laboratory finding in patients with spinal infection [59,121]. With normal values ( $4-11 \times 10^3$ ) in 64.5% of our patients this study confirmed that statement.

There existed a significant correlation between the increase in WBC and CRP (*p-value* 0.000\*). The WBC is not particularly useful in making a diagnosis of spinal infection, but should be part of an infection/fever workup as it may provide some general guidance concerning the response to treatment.

The measure of CRP was widely variable (range 0.8-450). But when the levels of CRP as well as WBC were highly elevated, the spinal infections were more aggressive and showed systemic manifestations. This was observed in patients with multifocal and pyogenic infections with the highest levels of inflammatory parameters.

That the previously mentioned inflammatory parameters are not specific for the diagnosis of infection is underlined by the finding, that up to 9% of our patients had a normal value of CRP, 64.5% showed a normal leucocyte count and in 1.2% the sedimentation rate was not accelerated. Above that those values can be increased due to various diseases other than infections.

Normal values of these inflammatory parameters, especially CRP, in 9 % of our patients could be explained by depressed immunity of the patients, absent soft tissue affection (no abscess formation) or ischemic nature of the affected bone. Given the variability in the source(s) of infection, blood cultures, urinalysis, and urine for culture should be obtained in patients suspected of having a spinal infection.



## 5.4.2 Causative organisms

### ➤ Blood cultures

They allow early isolation of the organism in approximately two thirds of the patients [122-124]. *Nolla et al.* in 2003 described a variable positive blood culture ranging between 42% and 82% [118]. It reached 71.1% in this study (162 of 228 patients with body temperature of  $>38^{\circ}\text{C}$ ). Blood was sent for culture in all patients who had fever at the time of admission.

Positive results are related to bacteraemia in patients with systemic manifestations, high levels of inflammatory parameters, soft tissue involvement dominating the bony affection and to presence of abscess.

Identification of the possible causative organism before the definitive surgery may save time to effectively attack the bacteria with suitable antibiotic therapy especially if prerequisites for early surgical management are not available or non-operative treatment is planned.

### ➤ Cultures from operative biopsies

The success rate described for isolation of the causative organism (positive cultures) is variable and ranged between 49% and 82% [85,125]. Tissue cultures obtained directly from the site of infections are the gold standard for diagnosis. However, cultures have been falsely reported to be negative in up to 40% of the cases of infections. Some cases of false negative cultures include low grade infections, loculated infections such as abscesses and sterilization due to preculture antimicrobial therapy or organisms which need special cultures or prolonged periods for growing.

In this study, 67.5% of the cultures yielded positive results. This percentage was variable over the eleven years of the study and reached the highest level in the last year 2015 (79.5%). The reason may be mostly due to the introduction of new media to isolate specific organisms and increased orientation to the microbiological aspects of spinal infections.

Tuberculous infection of the spine represents about one third of all cases of extrapulmonary TB [10] and 50% of the musculoskeletal TB affects the spine [127]. It is the most common cause of specific spondylodiscitis [128]. Tuberculous spinal infection in this study was diagnosed only in 19 patients (3.2%); five of them were found to have a pyogenic infection on top. *Akbar et al.* [128] could not prove any increase in the tuberculous spondylodiscitis in a retrospective study of 221 patients over 19 years.

Fungal spondylodiscitis is relatively uncommon (0.5%- 1.6%) and affects mainly the immunocompromised patients. The diagnosis and treatment of this entity is challenging, requiring a multi-disciplinary team [129,130]. The species more frequently involved are *C. albicans* (62%), *C. tropicalis* (19%) and *C. glabrata* (14%) [131]. In this study, fungal infection was found in 7 patients (1.2%); one of them having it mixed with bacterial infection. As in the literature [130], laboratory results revealed elevated ESR and CRP, whereas the WBC was normal. Fungal infection remains a diagnostic and therapeutic challenge, which may result in important functional consequences.

With growing numbers of multimorbid immunocompromised elderly patients, the gram negative bacteria-caused-spondylodiscitis has increased. Infection of the spine with gram negative bacteria in patients younger than 50 years is very rare [118]. In this study, it has been diagnosed in 45 patients (7.5%), only 4 patients of them being younger than 50 years. In 44.4% of those patients, *E. coli* was the causative organism which is the common pathogen in of urinary tract infections (found as associated infection in most of those patients (*p-value* 0.000\*). The nearby lumbar spine was affected in more than two thirds of the patients.

Vertebral osteomyelitis is primarily a monomicrobial bacterial infection [28]; predominant pathogens are *Staphylococcus aureus*, coagulase negative staphylococci. Polymicrobial infections occur in less than 10 % of cases and are most likely resulting from contiguous spread [27]. In 22 patients (3.7%), more than one organism (polymicrobial) could be isolated from the site of infection. The most common comorbidities in those patients were DM in 16 patients (*p-value* 0.004\*) and the presence of bed sores (*p-value* 0.002\*). The incidence of polymicrobial infection may explain the different organisms obtained in the blood cultures and the operative biopsy and this necessitates obtaining biopsy from the infected site even if positive blood cultures and non-operative treatment is chosen. The specimen should be submitted to microbiological analysis, such as Gram smear, aerobic and anaerobic cultures, plus fungal culture, particularly for tuberculosis infections.

Most of the isolated organisms from the tissue culture were facultative anaerobes (*staph. aureus* in 201 patients of them). These organisms can grow without oxygen but use oxygen if it is present. This may be explain the higher incidence of pyogenic vertebral osteomyelitis in elderly patients with diminished blood supply of the osteoporotic bone.

Histopathology per se has a complementary value to microbiological culture in distinguishing pyogenic from granulomatous diseases [132,133,134] and is mandatory if tumorous lesions are suspected [135,136].

In this study, the histopathological examination of the obtained tissues was routinely done. It was valuable especially in the cases with negative culture to exclude a granulomatous infection. In 5 patients with mixed infection, in whom the bacterial culture revealed a non-specific organism, the histopathological examination showed tuberculous granuloma.

Yet, even with improved diagnosis tools and procedures, the delay in diagnosis remains an important issue. This review aims to highlight the importance of a methodological attitude towards accurate and prompt diagnosis using an algorithm to aid on spinal infection management.

In conclusion; the spinal infections have high morbidity and mortality rates and historically were devastating diseases. Elderly people are often multimorbid and immunosuppressed, so they are more susceptible to these infections. Thanks to the advent of new diagnostic techniques, multiple-drug antimicrobial chemotherapy and advances in surgical techniques the prognosis of these diseases in the recent years could be improved. Whole Spine MRI is mandatory to diagnose multifocal spinal infections and should be the routine diagnostic method.

In old patients with depressed immunity or ill-nourished bone, spinal infection cannot be excluded by normal inflammatory parameters. These infections in elderly patients are characterized by a high incidence of paralysis which reached up to 58% in patients older than 65 years. Thus, the gold standard is obtaining biopsy or swab from the affected area to isolate an organism.

The inflammatory parameters: CRP, ESR, and WBC are not specific, but they are very important to monitor the response to treatment. Up till now specific infection markers such as Procalcitonin (PCT), have a limited role in cases with localized infections and absent systemic manifestations. Cultures with "no growth" in patients with spinal infections are still representing a great challenge regarding precise treatment. Introduction of PCR to identify the causative organism rapidly seems to be a promising method.

## **6 Summary**

The aim of this study was to analyse the demographic, clinical, radiological and laboratory parameters in patients with haematogenous spinal infection and to study the effects of various causative organisms on these parameters.

Therefore, in this work we identified 600 patients over a period of eleven years who had attracted haematogenous spinal infection and evaluated their records retrospectively.

We found an increase in the mean age of the patients with spinal infection over the eleven years mostly due to increased life expectancy in the German population. Most of the patients in this study had medical comorbidities which may render the patients immunocompromised and more susceptible to infections.

The diagnosis of spinal infection in elderly patients is frequently delayed due to the predominance of degenerative spine disease. Spinal infection should be suspected especially in patients with increased back pain, fever and development of neurological deficit.

The incidence of neurological affection increases with age even if in absence of compressing intraspinal pathologies.

Unifocal infection is the most common form, but the multifocal affection of the spine is not uncommon: (11.3%). It should be excluded by routine use of the whole spine MRI. The latter is also the gold standard imaging modality in cases of epidural and psoas abscesses.

Though the inflammatory parameters are non-specific for infection they are important in the workup in cases of spinal infections. C-reactive protein is the most valuable parameter in predicting the ability to isolate a causative organism in most of cases.

Spinal infection is mostly caused by one organism, but in diabetic patients and those with bed sores polymicrobial affection should be considered. In the past, tuberculosis represented the major cause of spinal infection but nowadays it changes roles with pyogenic origin. Fungal spinal infection is very rare and represented 1.6% of all cases in this study.

The ability to identify a causative organism increased over the years of the study to 79.5%. The reason may be mostly due to the introduction of new media to isolate specific

organisms and increased orientation to the microbiological aspects of spinal infections. *Staph. aureus* remains the main causative organism of spondylodiscitis over the years of the study and also in all age groups. With growing numbers of multimorbid immunocompromised elderly patients, the spondylodiscitis caused by gram negative bacteria has increased, however in patients younger than 50 years still is rare.

The key stone in the diagnosis and treatment of cases of spinal infections is the identification of the causative organism from the site of infection. Bacterial cultures and histopathological tissue examination are complementary in distinguishing pyogenic from granulomatous diseases and are mandatory when tumorous lesions are suspected.

## 7 Zusammenfassung

Das Ziel der vorliegenden Studie ist die Analyse demographischer, klinischer, radiologischer und paraklinischer Parameter bei Patienten mit hämatogenen spinalen Infektionen sowie der Einfluss der verschiedenen zugrundeliegenden Erreger auf diese Parameter.

Zu diesem Zweck konnten 600 Patienten mit hämatogenen spinalen Infektionen aus einem Zeitraum von elf Jahren retrospektiv in die Studie eingeschlossen werden. Es erfolgte die Analyse der entsprechenden Daten aus Aufzeichnungen der Krankenakten sowie dem radiologischen Bildarchiv.

Es konnte ein Anstieg des mittleren Alters der Patienten zum Zeitpunkt der Erkrankung über den Zeitraum der elf Jahre verzeichnet werden. Dies ordneten wir einem generellen Anstieg der durchschnittlichen Lebenserwartung der Bevölkerung zu. Die Mehrzahl der Patienten litt an relevanten Komorbiditäten – dies mag einen Einfluss auf die Immunkompetenz und somit die Erkrankungsanfälligkeit haben.

Die Diagnose von spinalen Infektionen ist bei Patienten im höheren Lebensalter häufig verzögert durch vorbestehende degenerative Wirbelsäulenveränderungen. Infektionen der Wirbelsäule sollten differentialdiagnostisch in Erwägung gezogen werden bei Patienten mit zunehmenden Rückenschmerzen, Fieber und dem Auftreten von neurologischen Defiziten. Die Inzidenz neurologischer Beeinträchtigungen steigt mit zunehmendem Lebensalter, auch ohne intraspinale Pathologien, die nervale Strukturen komprimieren, an.

Unifokale Infektionen lagen am häufigsten vor, ein Befall mehrerer Lokalisationen ist jedoch nicht ungewöhnlich (11,3%) und kann mittels routinemäßig durchgeführter MRT der gesamten Wirbelsäule ausgeschlossen werden. Die Kernspintomographie stellt auch den Goldstandard in der Diagnostik epiduraler Abszesse und von Psoasabszessen dar.

Obwohl Inflammationsparameter bei spinalen Infektionen unspezifisch erhöht sind gehören sie zum diagnostischen Basisprogramm. Das C-reaktive Protein erwies sich in der vorliegenden Studie als tauglicher Parameter, um die Wahrscheinlichkeit des mikrobiologischen Nachweises eines verursachenden Keimes abschätzen zu können.

Spinale Infektionen sind meist durch einen solitären, auslösenden Keim verursacht, bei Patienten mit Diabetes mellitus oder Decubitalulzerationen sind Mischinfektionen häufiger anzutreffen. In der Vergangenheit stellten tuberkulöse Spondylodiscitiden den Großteil spinaler Infektionen dar, heutzutage dominieren pyogene bakterielle Infektionen. Pilzinfektionen stellen mit 1,6% der Fälle in dieser Studie eine Rarität dar.

Die Wahrscheinlichkeit den verursachenden Keim zu isolieren stieg im Laufe des betrachteten Zeitraumes auf 79,5% an. Dies mag an neueren Kulturmedien im Nachweisverfahren und einer im Laufe der Zeit generell gestiegenen Aufmerksamkeit für die Diagnostik spinaler Infektionen liegen. *Staphylococcus aureus* bleibt über den Betrachtungszeitraum der am häufigsten isolierte Keim, dies ließ sich für alle Altersgruppen nachweisen. Mit steigendem Anteil multimorbider, immunkompromittierter älterer Patienten geht eine steigende Häufigkeit durch gram-negative Bakterien verursachter spinaler Infektionen einher, die bei Patienten unter 50 Jahren sehr selten anzutreffen sind.

Den Schlüssel in der Diagnostik und Therapie spinaler Infektionen stellt der Nachweis des verursachenden Keimes aus dem Ort der Infektion dar. Die histopathologische Untersuchung von Gewebeproben aus dem Fokus ist hilfreich in der Unterscheidung granulomatöser von pyogenen Infektionen und therapeutisch relevant im Falle eines negativen mikrobiologischen Keimnachweises sowie bei vermuteten neoplastischen Veränderungen.

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## **9 List of abbreviations**

<b>AP</b>	anteroposterior
<b>ASA</b>	American Society of Anaesthesiologists
<b>ASIA</b>	American Spinal Injury Association
<b>B.C.</b>	before Christ
<b>BCG</b>	Bacillus Calmette-Guerin vaccine
<b>BMI</b>	body mass index
<b>C.</b>	Candida
<b>COPD</b>	chronic obstructive pulmonary disease
<b>CRP</b>	C-reactive protein
<b>CT</b>	computerized tomography
<b>CV</b>	cerebrovascular
<b>DM</b>	diabetes mellitus
<b>E. coli</b>	Escherichia coli
<b>ESR</b>	erythrocyte sedimentation rate
<b>FSU</b>	functional spinal unit
<b>GIT</b>	gastrointestinal tract
<b>HIV</b>	human immunodeficiency virus
<b>ICU</b>	intensive care unit
<b>M.</b>	Mycobacterium
<b>M: F</b>	male: female
<b>MISS</b>	minimal invasive spine surgery
<b>MRI</b>	magnetic resonance imaging
<b>MRSA</b>	methicillin-resistant Staphylococcus aureus
<b>OI</b>	other infections
<b>PCT</b>	Procalcitonin
<b>Preop.</b>	preoperative
<b>PSI</b>	pre-surgical interval
<b>SD</b>	Spondylodiscitis
<b>Staph.</b>	Staphylococcus
<b>Strept.</b>	Streptococcus
<b>TB</b>	tuberculosis
<b>UTI</b>	urinary tract infection
<b>WBC</b>	white blood count

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## **Danksagung**

Für die jederzeit freundliche Betreuung und tatkräftige Unterstützung sowie die lehrreichen und amüsanten Stunden mit viel Diskussionsstoff bedanke ich mich bei meinen Betreuern Herrn Chefarzt PD Dr. med. H. Böhm und Herrn Univ.-Prof. Dr. med. Dr. h.c. C. Heiß.

Weiterhin möchte ich mich bei dem gesamten Team der Zentralklinik Bad Berka insbesondere Chefarzt Prof. M. Shousha für die tolle Zusammenarbeit und Unterstützung.

Sehr dankbar bin ich der Arbeitsgruppe der Asiut-Universität für die tatkräftige Unterstützung (Prof. M. El-Meshtawy, Dr. A. Shawky, Prof. F. F. Adam, Prof. M. G. Hasan, Prof. K. Younes und Prof. T. El-Gammal).

Ein großes Dankeschön geht an die Bibliothekarinnen Frau Stahl und Frau Züllinger für die Unterstützung bei der Literaturbeschaffung für diese Arbeit.

Nicht zuletzt danke ich allen meinen Lieben für Ihre Hilfe und insbesondere meinem Vater und Mutter sowie meiner Frau und meinen Kindern.

**Der Lebenslauf wurde aus der elektronischen  
Version der Arbeit entfernt.**

**The curriculum vitae was removed from the  
electronic version of the paper.**

**Internationale Vorträge und Poster:**

- 1- An alternative solution for elderly and polymorbid patients with lumbar spondylodiscitis.**  
H. Abdelrahman, A. Siam, H. Boehm. *SICOT 2012, Dubai.*
  
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