Non-Operative Management of Spinal Epidural Abscess: Development of a Predictive Algorithm for Failure

Abstract

Background context

Prompt diagnosis and treatment is key in spinal epidural abscess (SEA), as delay can lead to paralysis or death. The initial management decision for SEA is not always clear, with the literature showing conflicting results. When considering non-operative management, it is crucial to avoid failure of treatment, given the significant neurologic compromise incurred through failure. Unfortunately, data regarding risk factors associated with failure are scarce.

Purpose

The purpose of this study is to identify independent predictors of failure of non-operative management. Furthermore, we aim to develop a predictive algorithm that generates a probability of treatment failure based on the presence of these predictors.

Methods

All patients admitted to our hospital system with a diagnosis of SEA from 1993 to 2016 were identified. Patients older than 18 years who were initially managed non-operatively were included. Explanatory variables and outcomes were collected retrospectively. Bivariate and multivariable analyses were performed on these variables to identify independent predictors of failure. A nomogram was constructed to generate a risk of failure based on these predictors.

Results

We identified 367 patients who initially underwent non-operative management. Of these, 99 patients failed medical management. Multivariable logistic regression yielded six independent predictors of failure. Presenting motor deficit, pathologic/compression fracture in affected levels, active malignancy, diabetes mellitus, and sensory changes were positive predictors. Location of the abscess dorsal to the thecal sac was a negative predictor. Furthermore, we constructed a nomogram that generates a numerical probability of failure based on the presence of these factors. The presence of each

independent predictor is assigned a point value. The points are summed and the total is converted to a probability of failing non-operative management.

Conclusions

By quantifying the risk of failure based on the presence of six independent predictors of treatment failure, our nomogram may provide a useful tool for the treatment team when weighing the risks and benefits of initial non-operative versus operative management.

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Glossary

SEA: spinal epidural abscess

MRI: magnetic resonance imaging

CT: computed tomography

BMI: body mass index

WBC: white blood cell

ESR: erythrocyte sedimentation rate

CRP: C-reactive protein

AIC: Akaike Information Criteria

AUC: area under the receiver operating curve

CI: confidence interval

Introduction

First described by Morgagni in 1769 and defined by Bergamaschi in 1820, SEA occurs within the spinal epidural space between the dura and vertebral periosteum[1–4]. Microorganisms enter the epidural space through contiguous spread from a primary spinal infection such as spondylodiscitis, hematogenous dissemination from another infection (e.g. infectious endocarditis, pneumonia), or through direct external inoculation[1,5]. A suppurative process within the confined spinal canal may result in spinal cord or nerve root injury with subsequent neurologic dysfunction or paralysis. Unfortunately, the incidence of SEA has been increasing in the past several decades, rising from 0.2-2.0 cases per 10,000 hospital admissions in the 1950s-1990s to 2.5-5.1 cases per 10,000 admissions[1,6,7]. The rising incidence is likely multifactorial; an aging population with chronic disease, increased prevalence of intravenous drug use and alcohol abuse, improved diagnostics, and a growing number of patients undergoing spinal procedures and spinal instrumentation are contributory[1–3,6–9].

Most patients with SEA suffer from one or more predisposing conditions. Associated with reduced immunocompetence, diabetes mellitus is the most commonly observed risk factor for the development of SEA[2,10–13]. Intravenous drug use and alcohol abuse are also associated with SEA formation. Contaminated needles are common and patients who chronically inject heroin have diminished humoral and cellular immunity, as do patients suffering from chronic alcohol abuse[2]. Invasive spinal procedures represent an important SEA risk factor, creating a mode of entry for microorganisms into the epidural space[1,2]. Multiple cases of cervical and lumbar SEA after transforminal epidural steroid injections have been reported[14,15].

Prompt diagnosis confirmed by gadolinium-enhanced MRI with subsequent treatment is key in SEA, as delay can lead to paralysis or death[1–3,10,16]. Despite advances in imaging, SEA remains difficult to diagnose[1,2,10,11,17–19]. Its low incidence and non-specific presentation – back pain, fever, leukocytosis, increased inflammatory markers – make accurate diagnosis elusive. As many as 75% of SEA cases are misdiagnosed in the emergency department with resulting diagnostic delay[17,20,21]. Patients who are afebrile without elevated inflammatory markers or leukocytosis are often misdiagnosed with more common causes of back pain such as intervertebral disc herniation or degenerative joint disease. Even patients with an infectious presentation (e.g. fever, leukocytosis, bacteremia) may be misdiagnosed with more common conditions such as vertebral osteomyelitis, discitis, urinary tract infection, or infectious

endocarditis[1]. Despite its low sensitivity, many clinicians still rely upon the classic diagnostic triad of focal spine pain, fever, and neurologic deficit[7,13,17,22]. Many SEA cases are not identified until a neurologic deficit is present, delaying treatment of this dangerous entity[17].

There is considerable debate over whether the pathophysiology underlying neurologic deficit in SEA involves mechanical compression or cord ischemia through vascular occlusion[10,23]. In a rabbit model, histopathologic changes in the spinal cord seemed to be a result of direct compression rather than cord infarction[23,24]. Similarly, the fact that surgical decompression can often reverse motor deficits suggests a mechanical pathophysiology. On the other hand, the observation that neurologic deficit is often disproportionate to the degree of cord compression noted on imaging is suggestive of infarction secondary to thrombosis or thrombophlebitis[10]. A combination of mechanical cord compression and vascular damage with resultant ischemia is likely to be responsible[1,11,23,24].

Due to the risk of neurologic compromise from purulent expansion, timely treatment of suspected SEA is key. For much of the 20th century, urgent surgical decompression with systemic antibiotic therapy was considered the gold standard for SEA management[4,6,10,11,22,25]. Indeed, modern treatment algorithms for spinal infection indicate that the presence of an epidural abscess necessitates surgery[5]. With the earlier diagnosis afforded by advances in imaging, some have suggested that non-operative management – systemic antibiotic therapy with or without CT-guided percutaneous abscess drainage – may be a valid treatment option for SEA in certain cases[10,25–27]. There have been a number of reports of successful medical management in recent decades[3,9,18,26,28–33], as well as cases of successful percutaneous drainage[34–36]. These studies recommend closely following patients who are managed non-operatively. Disease progression including neurologic compromise, spinal instability, severe spinal angulation, and sepsis can be precipitous and unpredictable[1,11]. While some authors have posited general indications for non-operative management – poor surgical candidacy, extensive panspinal infection, absence of significant neurologic deficit, complete paralysis for >3 days – the relatively low number of cases in these reports has limited the identification of predictors of successful medical management[28,37].

Studies comparing the efficacy of operative and non-operative management have not provided much clarity due to conflicting conclusions. In their cohort of 33 patients with SEA, Siddiq and colleagues found medical management to be comparable to surgical management[31].

Similarly, Karikari et al. found no added benefit to surgery versus conservative management in 104 patients treated for SEA over a 10-year period[38]. In 82 patients aged 50 years or older, early surgical decompression with systemic antibiotics was not associated with superior clinical outcomes compared to antibiotic therapy alone[9]. Yet in a study by Curry and colleagues, the only significant predictor of positive outcome was the initial treatment modality; patients treated surgically had superior outcomes to those treated medically[22]. In line with this, Alton et al. strongly recommended early surgical decompression for SEA of the cervical spine, finding that delays in surgery can lead to neurologic deficits[39].

In addition to conflicting reports in the literature, it is difficult to determine the efficacy of non-operative management since successful cases are selectively reported and unsuccessful attempts are rarely reported after a decompressive laminectomy is performed[1,37]. Further complicating the decision of initial operative versus non-operative management is the paucity of studies investigating the risk of failure of non-operative management. When considering non-operative management, it is crucial to avoid failure of management given the significant neurologic compromise incurred through failure[39,40]. In an analysis by Patel et al., surgical treatment led to a statistically significant improvement in motor scores and successful non-operative management led to an insignificant improvement. Notably, patients who failed non-operative management suffered a mean deterioration in motor function significantly worse than the mean improvement of immediate surgery[40].

Despite the clear danger of failure of non-operative management, data regarding risk factors associated with failure have remained scarce. Recent studies by Kim et al. and Patel et al. identify potential predictors of failure of non-operative management and demonstrate the importance of stratifying patients to determine who is most likely to fail non-operative management[40,41]. In Kim et al., 2014, the authors conduct a retrospective, case-control study with 142 patients managed with initial non-operative treatment. They identify four independent predictors of failure of non-operative management: age older than 65 years, incomplete or complete spinal cord injury, diabetes mellitus, and methicillin-resistant *Staphylococcus aureus*. Furthermore, they provide an algorithm for the probability of failed antibiotic management based on the presence of these predictors[41]. In the same year, Patel and colleagues published a retrospective study of 51 patients with SEA managed non-operatively. Similar to Kim et al., they identify four independent predictors of management failure: diabetes, leukocytosis with WBC

count greater than 12.5 x 10^3 cells/microliter, positive blood cultures, and CRP greater than 115 milligrams/liter. They also provide a probability of failure based on the number of risk factors present[40].

Both Kim et al., 2014 and Patel et al., 2014 represent significant contributions to the SEA literature as they are the first studies with sufficient power to identify predictors of failure of non-operative management. By studying a dataset with a greater number of patients as well as including imaging data in addition to demographics and laboratory data, we hope that we can build on these studies' conclusions. We primarily aim to identify independent predictors for failure of non-operative management, providing guidance for when it may be acceptable to opt for non-operative management. Secondarily, we aim to develop a predictive algorithm that generates a probability of failure of non-operative management based on the presence of independent risk factors, providing a prognostic tool to clinicians trying to determine an initial treatment modality for SEA.

Materials and methods

Study design and subjects

Our institutional review board approved a waiver of consent for this retrospective study. We included patients 18 years and older diagnosed with SEA by MRI or CT in our hospital system of two tertiary academic medical centers and three regional community hospitals. We excluded patients who were initially treated operatively or who began treatment at an outside institution.

We identified our cohort by performing a computed query search of all patients admitted to our institution between 1993 and 2016 for International Classification of Diseases codes for SEA and synonyms (ICD-9 324.1, ICD-10 G06.1). We also performed a computed query search for Current Procedural Terminology codes for "laminectomy for excision or evacuation of intraspinal lesion other than neoplasm, extradural" (CPT 63275-63278). This initial search yielded 2,756 unique patients. Screening these medical records yielded 1,053 potentially eligible patients. For patients who presented with SEA on more than one occasion, the first encounter of non-operative management was included.

Of these 1,053 patients, 472 were initially treated non-operatively at the discretion of the primary attending physician. Here we define non-operative treatment as systemic antibiotic therapy with or without CT-assisted percutaneous drainage. Treatment groups were defined by the intention of the treating team: we considered the patient to have been treated non-operatively if the team initially elected for non-operative management. We exclude patients who were treated non-operatively for palliation or because they were too ill to undergo surgery. Only patients for whom the primary team decided non-operative management was the best treatment modality for eradicating the infection were included. The only patients in this analysis who underwent surgery for SEA were those who failed initial non-operative management and required subsequent surgery.

To avoid patients being prematurely labeled as having not failed treatment – as opposed to being in the process of failure when they were lost to follow-up – we only included patients without documented failure if they had more than 60 days of follow-up since initiation of treatment. If patients had less than 60 days follow-up but had a documented failure of treatment, they were included. This yields 367 patients (Figure 1).

Outcome and other variables

Our primary outcome measure was failure of non-operative management. Failure was defined as neurologic deterioration, worsened back/radicular pain, persistent symptoms, or progression on serial imaging despite initiation of antibiotic therapy. Non-operative management was only considered to have failed if it was initiated with the goal of successfully eradicating the infection. Radiologic progression of disease or worsening symptoms in a patient who was treated non-operatively for palliation or due to an inability to undergo surgery was not considered a failure.

For patients with multiple presentations for SEA, we carefully analyzed subsequent presentations to ensure that these did not represent treatment failures. Seven patients managed non-operatively had subsequent presentations for SEA not due to treatment failure with a median time between presentations of 48 weeks. Four subsequent abscesses were at different locations from the original presentation, one was due to a different microorganism, and one was an abscess that developed after surgery for an SEA that failed non-operative management. The remaining subsequent presentation was due to re-seeding of the epidural space by a fistula in the setting of metastatic rectal cancer.

We extracted the following explanatory factors from review of clinical notes: age, sex, BMI, social habits, medical comorbidities, previous spinal procedures or instrumentation, concurrent spinal infections, concurrent non-spinal infections, back/radicular pain, presenting motor function, bowel/bladder dysfunction, and sensory dysfunction. In terms of pre-treatment laboratory values, we collect WBC count, ESR, and CRP. Motor status was determined using the American Spinal Injury Association Scale[42]. Abscess characteristics and presence of concurrent spinal infections were determined from radiology reports. Blood and tissue culture data were obtained through microbiology reports.

Motor or non-motor neurologic deficits were scored as positive only if these were new symptoms. We define "sensory changes" to include frank sensory deficit as well as subjective paresthesias. Patients were considered to be immunocompromised if they had an immunosuppressive condition (e.g. human immunodeficiency virus, primary immunodeficiency) or were on immunosuppressive medications (e.g. chemotherapy, corticosteroids). Previous spinal procedures within one year prior to admission included any spinal surgery, implantation of epidural devices, and/or epidural steroid injection. An abscess was considered to be above the

level of the conus medullaris if the most caudal level of the abscess was above L1. If different organisms grew out of blood cultures and wound cultures, we deferred to wound culture data. An Infectious Diseases specialist reviewed all cultures containing organisms that were potentially contaminants to ensure they were the likely or confirmed SEA pathogen.

Statistical analysis

Categorical variables are provided with frequencies and percentages, and continuous variables with median and interquartile range. For nomogram construction, we randomly selected 80% of the cohort (294/367) to serve as our learning cohort and reserved the remaining 20% (73/367) as a validation cohort for internal validation.

Bivariate logistic regression was used to determine variables associated with failure of non-operative management. Stepwise backward logistic regression on bootstrap samples of the learning cohort (100 replications; full sample; with replacement) was used to determine variables eligible for inclusion in the multivariable model. Minimum AIC fit values were used to select the optimum multivariable model. We constructed the nomogram to predict a binary outcome of non-operative management failure using the average β coefficients of each predictor, determined by bootstrap analysis of the learning cohort (1000 replications; full sample; with replacement). Non-significant variables in the multivariable model were included to avoid against overestimation of the significant variables and to preserve predictive accuracy[43–45]. Model discrimination and calibration were determined using the AUC and the Hosmer-Lemeshow test.

We performed internal validation using bootstrap analysis of the validation cohort with equally sized random samples of the learning cohort (1000 replications; full sample; with replacement). Internal validation was achieved if the AUC and the regression coefficients for the validation sample fell within the 95% CI of the primary sample.

P values below 0.05 were considered significant. We used Stata 12 SE (StataCorp LP, College Stations, Texas, USA) for statistical analyses and nomogram construction.

Results

Demographics

Our cohort of 367 patients had a median age of 59 years (IQR 49-71) with 237 males (65%). In terms of social habits, 72 patients (20%) had a history of intravenous drug use. The most common observed medical comorbidity was diabetes mellitus, with 82 patients (22%). Twenty-five patients (6.8%) had an active malignancy at the time of presentation. Fifty-six patients (15%) were immunocompromised and 20 (5.5%) underwent regular hemodialysis for end-stage renal disease (Table 1).

Forty-one patients (11%) had a spinal procedure within one year prior to presentation; 20 (5.5%) had spinal instrumentation in place at the time of diagnosis. Seventeen patients (4.6%) had a pathologic or compression fracture in the affected area (Table 1).

The median WBC count was 10.4 x 10^3 cells/microliter (IQR 7.6-14.1). Median levels of inflammatory markers ESR and CRP were elevated at 87 millimeters/hour (IQR 53-106) and 100 milligrams/liter (IQR 32-164), respectively.

Presentation and abscess characteristics

Three hundred and fifty-three patients (96%) presented with back pain and 83 (23%) were febrile on presentation. Three hundred and three patients (83%) had normal motor function at presentation and 54 (15%) had a motor deficit. With respect to non-motor neurologic symptoms, 43 patients (12%) had sensory changes, 15 (4.1%) had urinary incontinence/retention, and 8 (2.2%) had fecal incontinence/retention (Table 1).

Abscesses spanned a median of two vertebral levels (IQR 1-4) and were most commonly located in the lumbar spine, with 135 lumbar abscesses (37%). One hundred and eight abscesses (29%) were located above the conus medullaris. With respect to location within the spinal canal, 243 abscesses (67%) were located ventral to the thecal sac, 59 exclusively dorsal abscesses (16%), and 26 (7.1%) circumferentially surrounded the thecal sac. Three hundred and five patients (84%) had a ventral abscess component.

Two hundred and thirteen patients (58%) had blood cultures positive for bacterial growth. One hundred and fourteen patients (31%) had radiologically-retrieved cultures. Ninety-two percent of cultures were obtained prior to the initiation of antibiotic therapy. The most common causative organism was methicillin-sensitive *S. aureus*, with 124 cases (34%). Nine patients

(2.5%) had cultures that grew multiple organisms. Eighty-four patients (23%) had sterile cultures (Table 1).

The most common concurrent local spinal infection was spondylodiscitis, present in 212 patients (58%). As for non-spinal infections, 23 patients (6.3%) had concurrent infectious endocarditis (Table 1).

Failure of non-operative management

Ninety-nine patients (27%) failed non-operative management. Sixty-five (65%) of those who failed non-operative management subsequently underwent surgery. The most common reason for surgery following failure was radiologic disease progression (46%), followed by neurologic deterioration (25%). Persistent or worsening symptoms and progressive deformity/instability were indications for surgery in 20% and 9.2%, respectively, of those requiring surgery after failure. The median time to failure was 25 days (IQR 11-37) (Table 2).

Bivariate and multivariable analysis

We performed bivariate logistic regression to assess association between explanatory variables and failure of non-operative management (Table 3). Minimum AIC fit criteria were used to select the best model, with an AIC value of 275. Multivariable analysis using the model selected by AIC fit criteria yielded six independent predictors of non-operative management failure (Table 4). Motor deficit at presentation ($p<0.001$), pathologic/compression fracture ($p=0.003$), active malignancy ($p=0.028$), diabetes mellitus ($p=0.001$), and sensory changes ($p=0.005$) are positive predictors of failure. Dorsal location of the abscess relative to the thecal sac is a negative predictor of failure ($p=0.014$) (Table 4).

Table 5 displays the prevalence of these six predictors in the failure and non-failure groups of the cohort.

Nomogram

We generated a nomogram using these six independent predictors from multivariable analysis. Each predictor is assigned a point value (Table 6). Although used to construct the nomogram, non-significant factors were not assigned point values. The points are summed and

the total is converted to a probability of non-operative management failure, calculated by the following algorithm:

$$Probability = \frac{e^{constant+\ (total\ points\ x\ points\ coefficient)}}{1 + e^{constant+(total\ points\ x\ points\ coefficient)}}$$

The constant is -1.95 and the points coefficient is 0.21.

Internal validation

The AUC for the primary sample with 95% CI is 0.82 (0.73-0.90) and the AUC for the validation sample is 0.82 (0.75-0.89). Hosmer-Lemeshow test for goodness of fit: 0.3969. All regression coefficients of the bootstrap sample were within the 95% CI of the primary sample.

Discussion

To our knowledge, our cohort of 367 patients represents the largest series of non-operatively managed patients with SEA from a single study. We collected data from 24 years of admissions at our hospital system comprised of two tertiary academic medical centers and three regional community hospitals. Our observational data are in line with previous reports in the literature with respect to patient age and male sex predominance, as well as SEA risk factors such as diabetes mellitus, intravenous drug use, heavy alcohol use, spinal intervention or deformity, immunosuppression, end-stage renal disease with hemodialysis, and trauma[1,2,4,6,10,17,22,46].

This study has limitations, first of which is its retrospective design. Second, extenuating circumstances sometimes dictated medical management. For instance, if a patient refused surgery, the treatment team was forced to opt for non-operative management. This may introduce selection bias in which patients underwent non-operative management. Furthermore, since most radiologic images were not available for review in our electronic medical record prior to 2007, abscess region and location relative to the thecal sac in these cases were based solely on radiology reports. Finally, a study on failure of non-operative management depends on clinicians making an incorrect judgment on a patient's predicted clinical course. Whenever a treating physician decides to proceed with non-operative management, he/she is weighing the risk of treatment failure against the benefit of avoiding spinal surgery. If a patient has a seemingly obvious risk factor for failure, the physician may be less likely to suggest non-operative management. Thus the population in whom we study failure will have a low rate of that risk factor, having the unintended effect of inhibiting our ability to identify a true predictor of failure. This may also have the effect of artificially inflating the importance of another risk factor.

The mainstay of SEA treatment has long involved prompt surgical decompression with drainage of pus and/or debridement of infected granulation tissue followed by systemic antibiotic therapy[1,6,10,12,22]. With advances in antibiotic therapy and the feasibility of following disease progression with serial MRI, non-operative management of SEA has become a viable treatment option[3,9,18,26,28–33]. Nonetheless, data comparing non-operative and operative management are not conclusive. A number of studies have compared the two with some advocating for surgical decompression, others for non-operative management, and still others claiming no difference between operative and non-operative management[3,6,9,10,22,30,31,38,39,47].

Complicating the initial management decision is the dire prognosis of patients who fail non-operative management[22,40]. Failure rates range from 6-49% in a recent systemic review[4]; our rate of 27% is in line with this. It is essential that clinicians are cognizant of risk factors for failure. In a rigorously performed analysis of 142 non-operatively managed patients from a series of 355 patients, Kim and colleagues identified four independent predictors of failure: age greater than 65 years, diabetes mellitus, methicillin-resistant *S. aureus* infection, and neurologic deficit involving the spinal cord[41]. From a series of 128 patients with SEA, Patel and colleagues studied 51 patients managed non-operatively. They identified four independent predictors of failure: diabetes, WBC count >12.5, positive blood cultures, and CRP greater than 115[40].

Our study has a series of 1,053 patients with SEA, from which we focus on 367 non-operatively managed patients. In addition to analyzing a larger study population, we build on the aforementioned studies by collecting more explanatory variables. We collect demographic data, past medical history, clinical presentation characteristics, laboratory data, as well as detailed information about the location and microbiology of the abscesses. We also focus on the anatomy of the abscess within the spinal canal; that is, whether the abscess is dorsal, ventral, or circumferential to the thecal sac.

Using a multivariable logistic regression model, we identify six predictors of failure of non-operative management. Like Kim and colleagues, we identified pre-treatment motor deficit as a risk factor for non-operative failure. Neurologic status is a key prognostic factor in SEA, with poorer outcomes observed in patients who present with motor deficit[2,6,10,11,17,21,25,41]. Indeed, approximately 90% of SEA patients are left with residual weakness when motor deficits are present at the time of diagnosis[2,6,17]. As in Kim et al., pre-treatment motor deficit is the most important risk factor for failure of non-operative management in our analysis, with the highest odds ratio of all the predictors. The presence of a motor deficit at presentation alone confers a 54% risk of failure. Despite the importance of obtaining an accurate neurologic exam, Davis and colleagues note that motor strength was documented in only 75% of emergency department physical exams in patients with SEA[17]. Not assessing for motor weakness in a quarter of patients risks missing valuable diagnostic and prognostic data.

We also identify presence of sensory changes as a risk factor for failure. Like motor weakness, the presence of either paresthesias or frank sensory deficit at presentation represents an advanced stage of disease with significant spinal cord injury[10]. Documenting non-motor

neurologic deficits is just as important as assessing motor strength. Only 67% of SEA patients in Davis and colleagues' study were initially assessed for sensory dysfunction, and less than half were assessed for rectal tone. Taken together with our findings, this underlines the importance of a comprehensive and accurate neurologic exam in any patient with suspected SEA. Differentiating between motor and non-motor neurologic deficits may allow clinicians to weigh the effects of different kinds of spinal cord injury when making an initial management decision, especially important given the variability of presentation for neurologic deficits in SEA[13].

Consistent with Kim et al., 2014 and Patel et al., 2014[40,41], we found that diabetes is predictive of treatment failure. Poor glycemic control has also been demonstrated to correlate with poor motor recovery after surgical treatment of SEA[48,49]. An established risk factor for the development of SEA, diabetes may adversely affect outcomes by impairing immune response and diminishing spinal microvasculature integrity[2,47,50]. Increased blood glucose levels are associated with reduced chemotaxis and phagocytosis of neutrophilic granulocytes[2]. We also found that an active malignancy at presentation is a predictor of non-operative management failure. Similar to diabetes, malignancy has a known immunosuppressive effect. Several tumor-derived factors inhibit dendritic cell maturation and T-cell activation[51], potentially complicating efforts to fully eradicate an infection.

The relationship between the local anatomy of the epidural space and neurologic outcomes has been previously studied. Surgically treated SEA of the thoracic spine have worse outcomes than in other spinal regions[6]. Various studies of metastatic spinal tumors and degenerative disease have also shown thoracic location to be associated with worse neurologic outcomes[52–54]. These findings may reflect the narrower spinal canal in this kyphotic region, making the thoracic spinal cord more susceptible to injury from compressive spinal pathology. Nonetheless, mechanical and anatomical factors have not been previously linked to failure of non-operative management. A mechanical factor that we found to be predictive of failure is presence of local pathologic/compression fracture. A risk factor for developing SEA, non-penetrating trauma may cause local inflammation or hematoma that can serve as a nidus for infection[2,13,29,55]. Furthermore, pathologic or compression fractures can cause local kyphotic deformity[56]. Similar to the rationale underlying worse neurologic outcomes in thoracic spinal pathology, this site of focal kyphosis may reduce the size of the epidural space in that area, allowing for purulent expansion to more readily cause neurologic dysfunction.

In addition to the local anatomy of the affected spinal region, the anatomy of the abscess within the spinal canal is an important risk factor for treatment failure. Some authors have found that there is no impact of abscess location relative to the thecal sac on outcome[41,57]. Others have found that dorsally located abscesses are independently associated with poor prognosis[9,38]. In their series of 104 patients with SEA, Karikari and colleagues report that dorsal abscesses are more likely to present with motor weakness and severe neurologic deficit than ventral ones. Since ventral SEA results from either spontaneous seeding of the ventral epidural fat or the disc space with extension into the epidural space, the authors reason that a ventral abscess is more likely to present with systemic symptoms before neurologic symptoms when compared to a dorsal abscess. As such, they hypothesize that a patient with a ventral SEA would present relatively early in the disease course and would thus be more likely to be successfully managed conservatively[38]. Contrary to this, we have found that an exclusively dorsal abscess is a negative predictor of failure of non-operative management. One must consider the avoidance of vascular compromise in the relatively protective effect we observe with primarily dorsal abscesses. Coursing along the ventral aspect of the spinal cord, the anterior spinal artery is the primary blood supply to the cord[58]. Disruption of the anterior spinal artery by a ventral abscess component may cause cord ischemia and worsened disease. While undoubtedly a high-risk condition, a purely dorsal abscess may pose less of a risk of compromise of this critical vessel from direct mechanical compression and/or infectious vasculitis compared to an abscess with a ventral component. Furthermore, a circumferential abscess may represent a more virulent or advanced disease process[41].

Predictive algorithm

Once the diagnosis of SEA is confirmed, a pressing question the clinician must answer is which treatment modality to pursue. Given the scarcity of data regarding failure of medical management, it is difficult for clinicians to make a data-driven treatment decision. Using six independent risk factors of failure of non-operative management, we have constructed a predictive algorithm that generates an individualized probability of failure for a given patient with SEA.

To illustrate the utility of the algorithm, we provide patient examples of how a treatment team could use it. Patient 1 is a 71-year-old man with a history of diabetes who presents with

three days of progressive lower extremity weakness. MRI reveals a L3-L5 dorsal SEA. The patient receives 10 points for presenting motor deficit, 5.1 points for diabetes, and -6.2 points for a dorsal location of the abscess. This gives a total of 8.9 points, which corresponds to a 48% risk of non-operative management failure. This example demonstrates the relatively protective nature of a dorsal abscess versus one with a ventral component. If the abscess were not located dorsal to the thecal sac, the patient would have a 77% risk of failure.

Patient 2 is a 68-year-old woman with metastatic breast cancer who presents with one week of mid-back pain. She has full strength in the upper and lower extremities bilaterally. MRI reveals a T8-T10 circumferential abscess with a T9 compression fracture. The patient receives 8.8 points for local compression fracture and 5.6 points for active malignancy. This gives a total of 14.4 points. Inserting this into the algorithm yields a 75% risk of non-operative management failure. Even in the absence of motor deficit, there may be a significant risk of failure in the presence of other independent risk factors. This is a notable finding, since lack of presenting motor deficit is often considered an indication for non-operative management[1,11,28,37].

Conclusions and future work

With the largest cohort of non-operatively managed patients with SEA, we identify six independent predictors of failure of non-operative management. These factors include measures of the patient's general health and neurological status at presentation as well as radiologic data and local abscess anatomy. While these predictors provide insight into drivers of poor outcome in SEA, simply identifying them does not provide maximal guidance to clinicians. In order to provide clinical utility, we include these factors in the construction of an algorithm that generates a patient-specific probability of treatment failure. By quantifying the risk of failure of non-operative management based on the presence or absence of independent risk factors, we are confident that our algorithm will provide a useful tool for the treatment team when weighing non-operative management for SEA.

It should be emphasized that our analysis does not make any conclusions regarding the efficacy of surgical management. Our study does not and cannot demonstrate that surgery would be more successful than non-operative management in those found to have a high probability of failure.

Through the use of separate learning and validation cohorts we have made every effort to ensure that our predictive algorithm is internally valid. Furthermore, as our data have been collected over 24 years in five different hospitals, we are confident that the conclusions of our study are generalizable. We nonetheless feel that the next important step for testing our algorithm's utility ought to be external validation on a dataset from another institution. Additionally, prospective randomized trials are necessary to evaluate the efficacy of predictors of non-operative management failure, as well as other outcomes of SEA.

Summary

SEA is a high-risk condition; purulent expansion within the confined spinal canal can lead to neurologic deficits, paralysis, or death. Yet its low incidence – reported at between 0.1-5.1 cases per 10,000 patients – has made it challenging to study with adequate statistical rigor. Prompt diagnosis and management of SEA is difficult due to its insidious and non-specific clinical presentation. After diagnosis, deciding upon the initial treatment modality poses a challenge to the treatment team. For much of the 20th century, surgical decompression and systemic antibiotic therapy was considered the treatment of choice for SEA. In recent decades, however, there have been numerous reported cases of successful non-operative management (i.e. systemic antibiotic therapy with or without CT-assisted percutaneous drainage). While a shift toward less invasive treatment modalities may spare patients the morbidity of unnecessary spinal surgery in certain cases, it is important to ensure that conservative management is effective in eradicating a patient's infection. Patients who fail non-operative management are likely to suffer worsened neurologic function. It is thus crucial to identify which patients are likely to fail medical management.

With the largest series of medically managed cases of SEA, we aimed to identify predictors of management failure. Within this cohort of 367 patients, 99 failed medical management. We split 80% of the population into a learning cohort and the remaining 20% served as a validation cohort. We then performed stepwise backward logistic regression in samples of the learning cohort, using minimum AIC fit values to select the optimum multivariable model. This yielded six independent predictors of failure of non-operative management: 1) motor deficit at presentation; 2) sensory changes at presentation; 3) diabetes mellitus; 4) active malignancy at the time of diagnosis; 5) pathologic/compression fracture in the affected area; 6) abscess located exclusively dorsal to the thecal sac.

Pre-treatment motor deficit and sensory changes both suggest an advanced disease stage with spinal cord injury. Motor deficit has been reported as a predictor for failure of non-operative management previously. Diabetes and malignancy are both known for their immunosuppressive effects. Diabetes in particular is a well-described risk factor for the development of SEA, and has also been previously noted as a risk factor for treatment failure. Local pathologic/compression fracture may cause an area of focal kyphosis, making purulent expansion in this area more likely to injure the spinal cord. Finally, we find that an abscess located dorsal to the thecal sac is

relatively protective against management failure. We hypothesize this may be due to a dorsal abscess' lesser likelihood of disrupting the anterior spinal artery and thereby contributing to cord ischemia.

Using these six predictors, we generated a predictive algorithm that generates a risk of failure of non-operative management. Each independent predictor was ascribed a point value. Based on the presence or absence of each predictor, a total number of points can be determined for each patient. The probability of failure can then be calculated from the algorithm. By quantifying the risk of failure of non-operative management, we are hopeful that our algorithm will provide a useful tool for the treatment team to make an initial management decision.

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Figure 1: Flow diagram detailing the inclusion and exclusion criteria that resulted in the final study population.

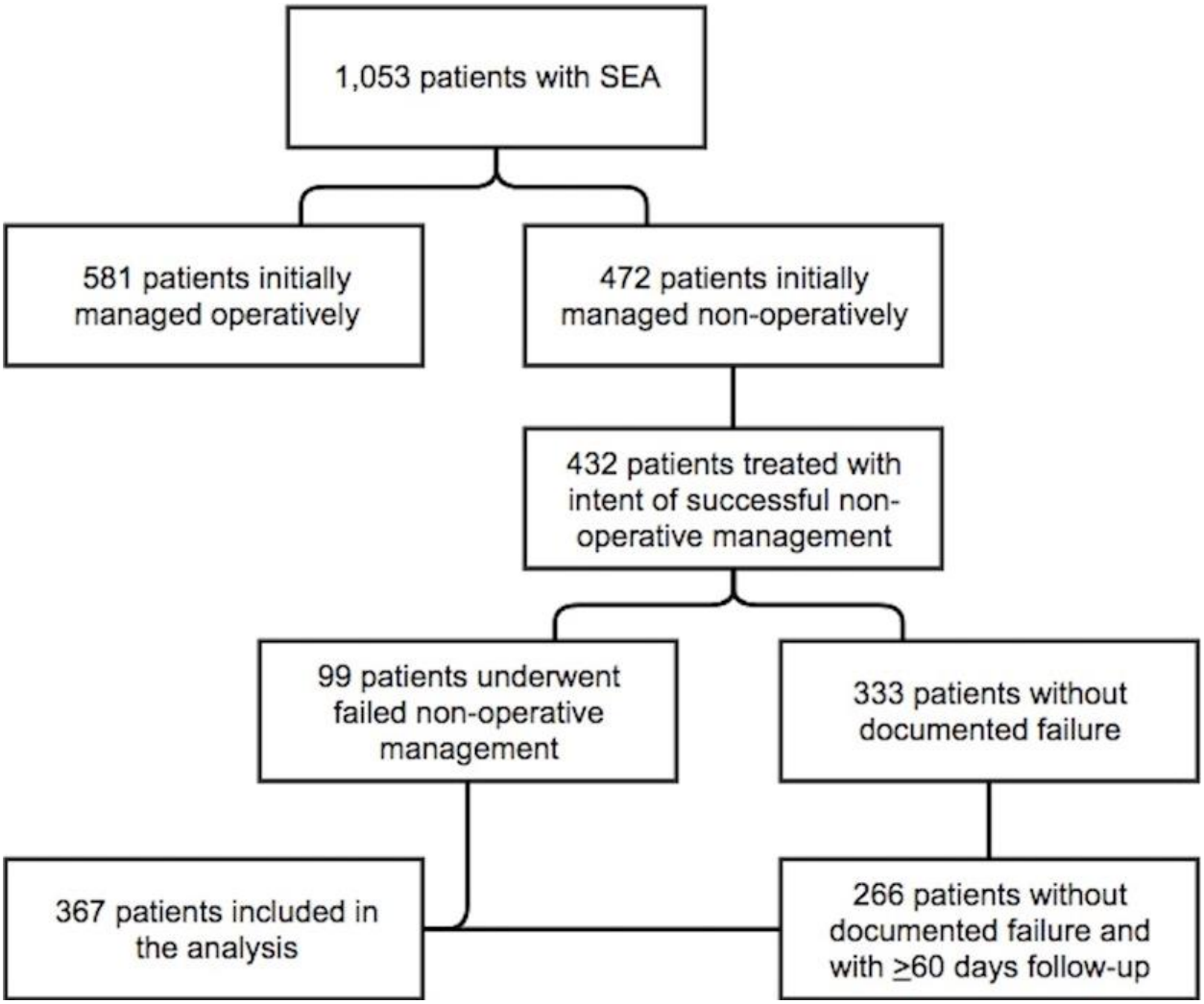

Table 1. Observational data	
Variable	**All Patients (n = 367)**
Demographics	
	Median (IQR)
Age (years)	59 (49 - 71)
	Number (%)
Male	237 (65)
Body mass index (in kg/m^2)†	
< 18.5	4 (1.1)
18.5 - 30	104 (28)
> 30	44 (12)
Habits	
Smoking	177 (48)
Intravenous drug use	72 (20)
Alcohol use	52 (14)
Medical comorbidities	
Diabetes mellitus	82 (22)
Immunocompromised	56 (15)
Active malignancy	25 (6.8)
Hemodialysis	20 (5.5)
HIV positive	12 (3.3)
Spinal instrumentation in place	20 (5.5)
Spinal procedure within 1 year prior to presentation	41 (11)
Spinal trauma	
Mechanical injury with no fracture	22 (6.0)
Pathologic/compression fracture	17 (4.6)
Mechanical fracture	8 (2.2)
	Median (IQR)
Laboratory values†	
White blood cell count (10/μL)	10.4 (7.6 - 14.1)
Erythrocyte sedimentation rate (mm/h)	87 (53 - 106)
C-reactive protein (mg/L)	100 (32 - 164)
Number of affected levels	2 (1 - 4)
Hospitalization duration (days)	12 (7 - 20)
Presentation	
Back pain	353 (96)
Fever	83 (23)
Motor function†	

Normal (ASIA E)	303 (83)
Incomplete injury (ASIA B, C, D)	48 (13)
Complete injury (ASIA A)	6 (1.6)
Sedated/existing deficit	9 (2.5)
Non-motor neurologic symptoms	
Radicular pain	268 (73)
Sensory changes	43 (12)
Urinary incontinence/retention	15 (4.1)
Fecal incontinence/retention	8 (2.2)
Symptom duration prior to presentation	
≤24 hours	24 (6.5)
24 - 72 hours	46 (13)
72 hours - 2 weeks	155 (42)
>2 weeks	142 (39)
Bacteremia	213 (58)
Fungemia	1 (0.3)
Abscess characteristics	
Region of spine	
Cervical	31 (8.5)
Cervicothoracic	12 (3.3)
Thoracic	68 (19)
Thoracolumbar	25 (6.8)
Lumbar	135 (37)
Lumbosacral	81 (22)
Sacral	2 (0.5)
Multifocal/non-contiguous	10 (2.7)
>2 contiguous regions	3 (0.82)
Above conus medullaris	108 (29)
Location of abscess relative to spinal cord†	
Ventral	243 (67)
Dorsal	59 (16)
Circumferential	26 (7.1)
Multiple locations	36 (9.9)
Ventral component to abscess	305 (84)
Organism	
No growth	84 (23)
Methicillin-sensitive staphylococcus aureus	124 (34)
Streptococci	39 (11)

Methicillin-resistant staphylococcous aureus	38 (10)
Coagulase-negative staphylococci	26 (7.1)
Mycobacteria	12 (3.3)
Escherichia coli	11 (3.0)
Multiple organisms	9 (2.5)
Enterococcus	6 (1.6)
Candida	3 (0.8)
Anaerobe	2 (0.5)
Pseudomonas aeruginosa	2 (0.5)
Other	11 (3.0)
Radiologically-retrieved cultures	114 (31)
Cultures obtained before initiation of antibiotics	339 (92)
Local spinal infections	
Spondylodiscitis	212 (58)
Psoas/paraspinal abscess	186 (51)
Vertebral osteomyelitis	50 (14)
Prevertebral abscess/retropharyngeal abscess	29 (7.9)
Discitis	20 (5.5)
Wound infection	15 (4.1)
Local non-spinal infections	
Infectious endocarditis	23 (6.3)
Non-spinal abscess/cellulitis	20 (5.5)
Septic arthritis	18 (4.9)
Pneumonia/empyema	13 (3.5)
Meningitis	6 (1.6)
Non-vertebral osteomyelitis	6 (1.6)
Other	12 (3.3)
	Number (%)
Failure of non-operative management	99 (27)
	Median (IQR)
Follow-up (weeks)	36 (17 - 115)

IQR = Interquartile range; mg/L = milligrams per liter; μL = microliter; mm/h = millimeters per hour; kg/m2 = kilogram per square meter; L = liter
† Body mass index was available in 152 cases (41%), ASIA scores were available in 366 cases (99.7%), location of abscess relative to the spinal cord was available in 364 cases (99%), erythrocyte sedimentation rate was available in 317 cases (86%), C-reactive protein was available in 248 cases (68%).

Table 2. Non-operative management failure characteristics	
Variable	**All Patients (n = 99)**
	Number (%)
Treatment after non-operative failure	
Operative	65 (65)
Non-operative	34 (35)
Reason for surgery after failure	
Radiologic progression	30 (46)
Neurologic deterioration	16 (25)
Persistent or worsening symptoms	13 (20)
Progressive deformity/instability	6 (9.2)
	Median (IQR)
Time to failure (days)	25 (11 - 37)

Table 3. Bivariate logistic regression assessing risk factors for failure of non-operative management

Explanatory variables (n = 367)	Odds Ratio (95% CI)	*p* value
Demographics		
Age (years)	1.02 (1.00 - 1.03)	0.042
Male	0.73 (0.45 - 1.17)	0.193
Body mass index (in kg/m^2)†		
< 18.5	4.20 (0.56 - 31.7)	0.164
18.5 - 30	*Reference value*	
> 30	0.79 (0.31 - 2.04)	0.633
Habits		
Smoking	0.96 (0.60 - 1.52)	0.862
Intravenous drug use	0.74 (0.40 - 1.36)	0.334
Alcohol use	2.25 (1.22 - 4.13)	0.010
Medical comorbidities		
Diabetes mellitus	2.93 (1.75 - 4.92)	<0.001
Immunocompromised	1.78 (0.98 - 3.23)	0.060
Active malignancy	2.25 (0.98 - 5.14)	0.054
Hemodialysis	1.48 (0.57 - 3.83)	0.418
HIV positive	1.36 (0.40 - 4.61)	0.624
Spinal instrumentation in place	1.48 (0.57 - 3.83)	0.418
Spinal procedure within 1 year prior to presentation	1.64 (0.87 - 3.11)	0.129
Spinal trauma		
Mechanical injury without fracture	0.83 (0.30 - 2.33)	0.725
Pathologic/compression fracture	4.16 (1.54 - 11.2)	0.005
Mechanical fracture	0.89 (0.18 - 4.50)	0.891
Presentation		
Back pain	1.38 (0.38 - 5.05)	0.626
Fever	0.69 (0.38 - 1.23)	0.207
Motor deficit at presentation	9.48 (4.95 - 18.2)	<0.001
Non-motor neurologic symptoms		
Radicular pain	1.18 (0.71 - 1.97)	0.521
Sensory changes	3.72 (1.94 - 7.15)	<0.001
Urinary incontinence/retention	7.36 (2.25 - 24.1)	0.001
Symptom duration prior to presentation†		
<24 hours	*Reference value*	
24 - 72 hours	0.97 (0.31 - 3.06)	0.959

72 hours - 2 weeks	0.82 (0.30 - 2.23)	0.694
>2 weeks	1.58 (0.59 - 4.24)	0.363
Bacteremia	0.97 (0.61 - 1.55)	0.905
Abscess characteristics		
Region of spine		
Cervical	0.37 (0.13 - 1.09)	0.072
Cervicothoracic	2.80 (0.88 - 8.88)	0.081
Thoracic	1.61 (0.92 - 2.83)	0.095
Thoracolumbar	1.29 (0.54 -3.09)	0.571
Lumbar	0.71 (0.43 - 1.16)	0.172
Lumbosacral	1.05 (0.60 - 1.83)	0.870
Multifocal/non-contiguous	1.16 (0.29 - 4.56)	0.836
>2 contiguous regions	1.35 (0.12 - 15.0)	0.809
Above conus medullaris	1.19 (0.73 - 1.96)	0.485
Location of abscess relative to thecal sac†		
Anterior	*Reference value*	
Posterior	0.49 (0.23 - 1.05)	0.065
Circumferential	1.99 (0.87 - 4.55)	0.105
Multiple locations	1.53 (0.73 - 3.20)	0.258
Ventral component to abscess	2.31 (1.09 - 4.90)	0.029
Organism		
No growth	0.70 (0.39 - 1.26)	0.233
Methicillin-sensitive staphylococcus aureus	0.77 (0.47 - 1.27)	0.308
Methicillin-resistant staphylococcus aureus	1.22 (0.59 - 2.52)	0.588
Streptococci	0.23 (0.43 - 1.96)	0.826
Coagulase negative staphylococci	1.95 (0.87 - 4.37)	0.103
Multiple organisms	3.48 (0.91 - 13.2)	0.067
Escherichia coli	0.59 (0.12 - 2.77)	0.503
Mycobacteria	0.89 (0.24 - 3.37)	0.866
Enterococcus	1.35 (0.24 - 7.49)	0.731
Anaerobe	2.70 (0.17 - 43.7)	0.483
Candida	1.35 (0.12 - 15.0)	0.809
Pseudomonas aeruginosa	1	
Other	1.01 (0.26 - 3.88)	0.991
Local spinal infections		
Spondylodiscitis	1.22 (0.76 - 1.96)	0.404
Psoas/paraspinal abscess	1.22 (0.77 - 1.94)	0.403
Vertebral osteomyelitis	0.97 (0.49 - 1.91)	0.920
Prevertebral abscess/retropharyngeal abscess	0.84 (0.35 - 2.04)	0.707

Discitis	1.61 (0.62 - 4.22)	0.332
Wound infection	1.84 (0.64 - 5.32)	0.259
Local non-spinal infections		
Infectious endocarditis	0.38 (0.11 - 1.32)	0.130
Non-spinal abscess/cellulitis	1.16 (0.43 - 3.11)	0.766
Septic arthritis	1.37 (0.50 - 3.74)	0.545
Pneumonia/empyema	0.80 (0.22 - 2.97)	0.739
Meningitis	0.67 (0.07 - 6.05)	0.720
Other	0.89 (0.24 - 3.37)	0.866
White blood cell count (10/μL)	0.99 (0.95 - 1.02)	0.532
Erythrocyte sedimentation rate (mm/h)	1.01 (1.00 - 1.01)	0.090
C-reactive protein (mg/L)	1.00 (1.00 - 1.00)	0.468
Number of affected levels	1.03 (0.94 - 1.12)	0.513

CI = Confidence Interval; mg/L = milligrams per liter; μL = microliter; mm/h = millimeters per hour; kg/m2 = kilogram per square meter; L = liter
† Body mass index was available in 152 cases (41%), location of abscess relative to the spinal cord was available in 364 cases (99%), erythrocyte sedimentation rate was available in 317 cases (86%), C-reactive protein was available in 248 cases (68%).

Table 4. Multivariate logistic regression assessing risk factors for failure of non-operative management

Explanatory variables (n = 367)	Odds Ratio (95% CI)	*p* value
Motor deficit at presentation	7.85 (3.69 - 16.7)	**<0.001**
Pathologic/compression fracture	6.12 (1.86 - 20.1)	**0.003**
Active malignancy	3.32 (1.14 - 9.64)	**0.028**
Diabetes mellitus	2.94 (1.53 - 5.65)	**0.001**
Sensory changes	3.48 (1.45 - 8.35)	**0.005**
Location of abscess relative to thecal sac		
Anterior	*Reference value*	
Posterior	0.29 (0.11 - 0.78)	**0.014**
Circumferential	1.48 (0.52 - 4.18)	0.463
Multiple locations	1.30 (0.47 - 3.60)	0.614

Bold indicates significance (P value less than 0.05). CI = Confidence Interval

Table 5. Independent predictors of failure of non-operative management		
	Failure (n = 99)	**Non-failure (n = 268)**
Motor deficit	37 (38)	17 (6.3)
Pathologic/compression fracture	10 (10)	7 (2.6)
Diabetes mellitus	37 (38)	45 (17)
Sensory changes	23 (23)	20 (7.5)
Dorsal abscess	9 (9.2)	50 (19)

Table 6. Points per predictor	
Predictor	**Points**
Motor deficit at presentation	10
Pathologic/compression fracture	8.8
Sensory changes	6.1
Active malignancy	5.6
Diabetes mellitus	5.1
Dorsal location of abscess relative to thecal sac	-6.2