Chapter 12
Cervical Spine Disease in Elderly Patients with Ankylosing Spondylitis

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Background and Etiology

Ankylosing spondylitis (AS), also known as Bechterew's disease, is a type of peripheral or axial spondyloarthropathy (a heterogeneous group of rheumatic diseases with common clinical and genetic features). It is a common inflammatory, rheumatic autoimmune disease that affects the axial skeleton via chronic inflammation in the spine. These inflammations can lead to fibrosis and calcification, resulting in loss of flexibility, and fusion of the spine into an immobile element with a "bamboo" appearance. Inflammation of the sacroiliac joint also occurs [1].

Idiopathic seronegative involvement of the cervical and lumbar spine remains a pressing issue and complicates early radiographic and OPD diagnoses [2]. Main clinical manifestations include back pain and progressive spinal rigidity as well as inflammation of the hips, shoulders, peripheral joints, and fingers/toes. In addition, there are extra-articular manifestations, such as acute anterior uveitis, psoriasis, and inflammatory bowel disease (IBD). However, AS progression in the cervical spine

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remains inadequately addressed, as involvement is typically late but can predominate existing pain and other symptoms [3]. Ankylosing spondylitis of the cervical spine is associated with stiff kyphosis and increased risk of transversal unstable fracture. A spine surgeon may be involved mainly in the management of trauma cases, but in some situations, corrective surgery of a kyphotic cervical deformity is needed [3].

Immune cells and innate cytokines have been suggested to be crucial to the pathogenesis of AS, especially the human leukocyte antigen and the interleukin axis; however, the pathogenesis of AS remains unclear. Etiology of AS can be grouped into several categories, with main genetic factors being key areas of recent interest. One of the most important genetic factors is major histocompatibility complex (MHC) class I allele HLA-B27, which was discovered in 1973 [4]. Despite the unclear pathomechanism, HLA-B27 has been associated with the prevalence of AS in different populations around the world [5]. Studies have shown that 90–95% of AS patients are HLA-B27 positive, while 1–2% of HLA-B27-positive populations develop AS. This number increased to 15–20% for those with an affected first-degree relative [6]. The familial tendency of AS was remarkable with relative risks of 94, 25, and 4 for first-, second-, and third-degree relatives, respectively [6]. In addition to the association with the genesis of AS, HLA-B27-positive patients showed a significantly lower average onset age and a higher prevalence of acute anterior uveitis than did HLA-B27-negative patients [6].

Epidemiology and Risk Factors

Variations in AS prevalence depend on geography, demographics, and database information that represent diverse cohorts and study groups. A cross-sectional survey in 2012 estimated the prevalence of AS in the United States to be 0.9 to 1.4% of the adult population, similar to that of rheumatoid arthritis [7].

A more recent 2018 analysis of currently published epidemiological data, conducted by the Department of Rheumatology at Columbia University, on AS prevalence found a range of between 9 and 30 individuals per 10,000 persons [7]. Variations across different countries were reported as ranging from 9 individuals per 10,000 persons in a study conducted on two indigenous Oaxaca Mexican populations [8] to 14 to 48 individuals per 10,000 persons in two randomly selected Shantou Chinese populations [9].

In addition to established genetic risk factors involving more than 100 loci and the HLA B-27 marker, two additional studies mentioned in the 2018 review found significant factors associated with increased or decreased AS development later on in life.

Montoya et al. reported decreased AS incidence among breastfed individuals compared to their non-breastfed siblings. Of 203 study patients with AS, 57% were breastfed, compared with 72% of 293 unaffected siblings, indicating that breastfeeding was protective (odds ratio 0.53; 95% CI 0.36, 0.77) among candidates.

These findings suggest that early life gut microbiota cultivation may have protective benefits against AS development [10].

More research with long-term follow-up data is needed to better understand non-genetic factor effects on AS development across diverse demographic groups and geographic regions.

Medical Treatments for AS

Pharmacologic interventions focus on alleviating symptoms while reducing chronic inflammation and reducing radiographic progression rates. Traditional drugs aimed at treating AC have mainly revolved around the utilization of nonsteroidal anti-inflammatory drugs (NSAIDs), anti-TNF-α (TNFi) factors, and monoclonal antibody target therapies. However, recent developments in the realm of nanotechnology-driven drug delivery systems and in AI and technological modeling have shown promising results for AS management.

Tumor necrosis factors (TNF) belong to a group of pro-inflammatory cytokines with roles in AS pathways. Inhibiting TNF-mediated inflammatory pathways therefore prevent radiographic progression and alleviate symptoms even among cervically involved AS patients. Maas and colleagues investigated how TNF inhibitors (TNFi) affect the C-spine, with their results indicating that cervical facet joints and vertebral bodies decreased the ankylosing rate [11]. For nonresponsive NSAID patients, TNF inhibitor (TNFi) therapy not only effectively inhibits AS progression but also decreases inflammation via binding and blocking TNF cytokines, which recent studies have shown improves spinal mobility, pain, and fatigue. Common TNFi's used in late-stage AS to treat radiological cervical changes include adalimumab, etanercept, golimumab, and infliximab.

Infliximab is now approved in Europe for the treatment of AS patients with severe axial symptoms, elevated serological markers of inflammatory activity, and an inadequate response to conventional therapy. The first study to assess the effects of infliximab in AS patients was an open pilot trial of 11 individuals who were treated with 3 infusions of infliximab (at weeks 0, 2, and 6), in a dosage of 5 mg/kg. This study found improvement of ≥50% in activity, function, and pain scores in 9 of 10 patients. After 4 weeks, the median improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was 70%. These benefits lasted for at least 6 weeks [12].

Cervical Spine Fracture in the Elderly

Manifestations of AS typically begin before the third decade and present slow but steady progression [13]. Compared to the general population, patients with AS are at higher risk of spinal fracture and subsequent spinal cord injury (SCI) [14]. Spine

fractures in AS patients result in poorer outcomes due to systemic organ involvement of AS, with increased incidence of hypertension, cardiovascular mortality, and pulmonary disease. There is a fourfold increase in fracture risk among AS patients compared to the general population, with lifetime incidences of 5–15% [15]. The estimated vertebral fracture prevalence ranges from 4% to 18%, with annual an incidence up to 1.3% [16].

It is proposed that AS patients are prone to falling due to poor sagittal balance, pelvic retroversion, and altered knee bending and gait while walking. These conditions coupled with the compromised horizontal gaze due to kyphotic deformity, and other risk factors including old age, advanced disease, kyphosis and alcohol-use negatively impact balance [15]. Fusion of the cervical spine renders it vulnerable to trauma [17]. In a recent study using the nationwide inpatient sample (NIS) database from 2005 to 2011, 53% of fractures were located in the cervical spine, 41.9% were thoracic, 18.2% in the lumbar, and 1.5% in sacrum [18]. Most fractures were located on the vertebral level. Osteoporosis is another well-known complication of AS systemic involvement. Ligamentous ossification may occur on disc and joint capsules in AS patients. Weakened mechanical strength, especially on the vertebral level and the fracture on the vertebral level, should be considered as a combined result of osteoporosis and ligamentous ossification.

Unstable cervical fractures can still occur even after minor trauma or low energy impacts [17]. Low energy impacts such as falls from a standing or sitting position are a major cause of fractures (65.8%) in AS. Fractures mostly occur in the intervertebral disc (IVD) due to degradation of the IVD and chondroid metaplasia and loss of elasticity due to calcification of the annulus fibrosis, making IVD the weakest point of the AS spine [17]. Due to ligamentous ossification, injury often occurs as three-column injuries with unstable status [15]. Combined unstable fractures of the cervical spine and esophageal injuries have been reported in AS patients, even after minor trauma. A case report found during surgery the esophagus entrapped within the fracture, a relatively unusual presentation in AS-related fractures [19].

Neurological complications are common in AS-related fractures. AS with spinal fractures is highly associated with spinal cord injury (SCI). According to a large systemic review, SCI is present in 67.2% of spinal fractures within AS patients, with accompanying diverse neurologic function impairment [17]. SCI can be caused by dislocation, cord contusion or compression by fractured bone segments, ossified posterior ligamentum, herniated disc, or an epidural hematoma in AS patients with cervical spine fractures [15]. Secondary deterioration from collar usage, transportation, or manipulation in the posttreatment phase (after admission to posttreatment 3 months) is not uncommon, with a prevalence of 13.9% being reported in a corresponding systemic review [17]. Prognosis in AS patients with cervical fractures is relatively poor, with 6.4% and 11.3% mortality in surgically treated and conservatively treated patients, respectively, after short-term follow-up posttreatment. Also, the most relevant cause of mortality is pneumonia or respiratory failure [17].

Cervical fractures in AS patients can be easily overlooked due to chronic neck pain, or visual obfuscation by a humping shoulder on X-ray film, especially should the fracture take place at the lower cervical spine or cervicothoracic junction. Moreover, it is usually difficult to interpret the X-ray film due to distorted anatomy and osteoporosis in AS cases [15]. More than half of the cervical fractures were not discernible on C-spine X-ray film alone. Computed tomography (CT) scans should be routinely examined for any AS patient suspected of spinal fracture, while MRI can serve as an adjunct in evaluating soft tissue and spinal cord status, especially in patients suffering from neurological deficits [16].

There is an issue of delayed cervical fracture diagnoses in AS patients. Studies indicate that 17.1% of fractures are identified within 24 h following trauma. These fractures remain unnoticed until delayed development of neurological deficits present [17]. Delayed diagnosis may result from a history of rather minor trauma and difficulty in the interpretation of spinal radiographs.

The standard management of cervical fractures in AS patients include conservative and surgical treatments. Conservative treatments involve bed rest, Halo vests, collars, and orthosis. Most of the patients who undergo conservative management are mainly those at high surgical risk or who refuse aggressive management [17]. However, C-spine immobilization in unstable fractures is important in initial management. Careful evaluation of the preexisting spinal configuration is mandatory before applying a traditional collar, whereas inappropriate outfitting of traditional collars may cause hyperextension and further malpositioning of the fracture site, which in turn increases the risk of SCI [15]. Traction should be gentle, starting from low weight traction (<5 to 10 pounds), with force vectors directed anteriorly and superiorly [15]. Traction should be due to weakness of the paraspinal muscle and high instability. The head and upper back need to be supported by pillows or rolls in kyphotic cases [15]. The aim of traction is to restore previous alignment, which is usually kyphosis in AS patients, and to prevent secondary deterioration and facilitate fracture healing [15].

Surgery is usually inevitable in AS patients with cervical fractures. Surgical indications involve deterioration of neurological status, unstable fracture configurations, presence of epidural hematoma, or bony fragment compression that cause neurologic deterioration. Surgical choices vary according to patient condition. In an acute injury without significant deformity, one should consider treatment through anterior fusion or posterior fusion alone, depending on the fracture site. Acute and chronic injuries with deformities could first undergo light cervical traction for reduction. If the patient can remain prone, posterior fusion may be performed. Open reduction should be performed if close reduction with traction fails [20]. Sufficient decompressive laminectomy should be performed with a posterior approach if spinal cord compression is evident. Local bone harvesting for bone fusion is optional, while iliac crest bone grafts remain the gold standard for fusion material. The additional wound, however, may cause pain and immobilization that could lead to further complications. Thus, local bone harvesting from the spinous process for posterior approach cases, and allograft bone or cage with bone extenders for anterior approach cases, is also a viable option [20].

Anterior approaches can be difficult due to chin-on-chest deformities and potential blockage of surgical corridors. However, an anterior approach may be a viable choice if the patient cannot tolerate a prone position due to an AS-related cardiac-pulmonary condition [18]. Anterior fixation alone may result in implant loosening due to forces from the posterior column. A 50% failure rate for initial anterior fixation has been reported [18]. For posterior approaches, the number of fixations should be carried out at least two levels above and below. Long segment fixation provides the strongest stability [21]. Cervical pedicle screws allow the most powerful forces biomechanically, but are technically demanding. According to most studies, lateral mass screw fixation is strong enough. However, the construct should be extended below the cervicothoracic junction with thoracic pedicle screws in cases of lower cervical fractures, which are most of the cases where cervical fractures take place.

A combined anterior and posterior approach may be necessary when the spinal vertebral structure is significantly compromised, especially with marked kyphotic deformities at the fracture site (Fig. 12.1) [21]. However high pulmonary-related complication risks, probably due to longer surgical time and immobilization period, should be noted [18]. Some authors advocate circumferential fixation and fusion due to cervical fractures in AS always extending across anterior to posterior elements. A single approach may not be able to offer enough stability in most of the cases [21]. Poor bone quality in AS patients is also a

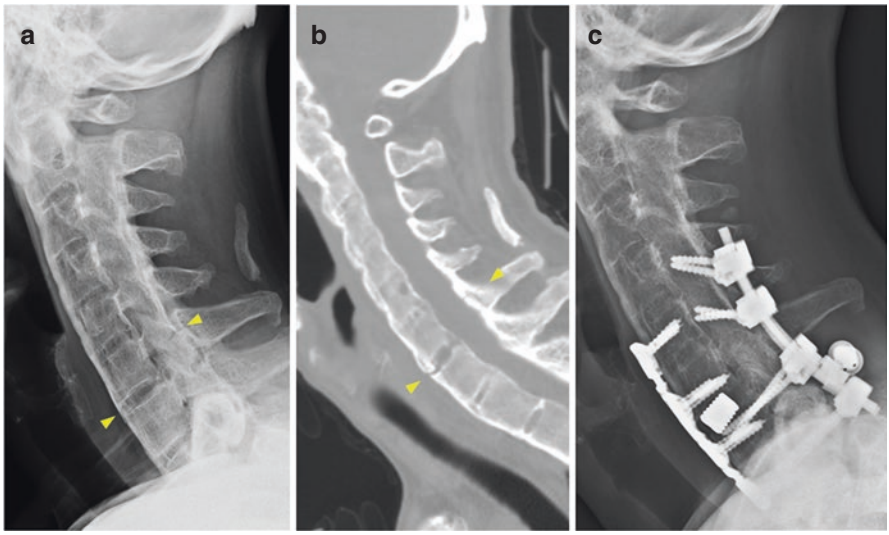

Fig. 12.1 A 54-year-old AS patient with a falling accident and severe neck pain. (**a**) Plain lateral film showed a subtle fracture over C6-C7 (arrow heads), which can be easily missed. (**b**) CT showed a three-column fracture from the C6-C7 intervertebral disc space to the C6 posterior column (arrow heads). (**c**) Plain lateral film after C6-C7 ACDF and C4-T1 posterior fixation. A long construct is often necessary for cervical fractures among AS patients

consideration for circumferential fixation. Etka et al. reviewed the NIS database from 2003 to 2014 and recognized a shift in surgical approaches from combined anterior and posterior fusion to posterior or anterior fusion alone, with posterior fusion being the most commonly performed option. In summary, the selected approach should be individualized, depending on fracture location and patient characteristics.

Overall, surgically treated patients are likely to have more neurologic improvements and less complications compared to nonsurgically treated ones. Surgical treatment is highly suggested for patients with unstable fractures or with neurological symptoms. A large retrospective review showed a mortality rate of 51% in the nonoperative group versus 23% in the operative group, with age >70 being a major risk factor [15]. Conservative treatments may lead to worse fracture healing with pseudoarthrodesis [18]. Surgical treatment for cervical fractures in AS patients remains challenging for spine surgeons. Osteoporosis and long lever length in such cases are more likely to result in instrument failure [20]. Comorbidity of AS, including aortic insufficiency, cardiac conduction abnormalities, uveitis and pulmonary disease, increase the surgical risk and lead to a higher complication rate postoperatively [15].

Cervical Deformity in the Elderly

Cervical kyphotic deformities in AS may be the result of prolonged and progressive postural flexion from spondylitic facet pain and auto-fusion in fixed flexion deformities. With the nature of osteoporosis, AS kyphotic deformities can also be aggravated by subtle cervical fractures that heal with poor alignment [22]. The kyphotic deformity can cause sagittal imbalance with general soreness and fatigue. In extreme cases a large chin-brow vertical angle (CBVA), so-called chin-on-chest deformities, difficulty of forward/upward vision and swallowing can further compromise patients' quality of life.

Flexion and extension radiographic films are often taken for the evaluation of remaining flexibility in fused AS spines or evaluation of subtle fractures with instabilities. AS disease progression and the ability to compensate should also be taken into consideration when making treatment plans. In general, treatment for AS deformity works under the same thinking processes, with treatment for adult spinal deformity taking precedence, along with taking global sagittal and coronal balance into consideration. Generally, AS patients with universal kyphosis and sagittal imbalances that need surgical correction and corrective hip surgery are first considered, followed by thoracolumbar deformity correction patients. Improvement in thoracic and lumbar alignment may significantly improve the T1 slope, C2-C7 SVA, and CBVA, thereby potentially sparing the need for further cervical kyphotic deformity surgery. However, correction of cervical kyphosis may still be indicated in AS patients without thoracolumbar (TL) deformities.

CBVA is the most important parameter for correcting AS cervical kyphotic deformity. Song et al. suggest a CBVA between 10° and 20° for optimal daily function and appearance [23]. Overcorrection of CBVA may also affect downward gaze and therefore compromise walking ability. However, the optimal CBVA should be tailored to meet individual needs. In addition to cervical/thoracic CT and MRI for preoperative planning, CT angiography is arranged for evaluation of vertebral artery courses in the evaluation of aggressive osteotomies. Cardiopulmonary function evaluation should also be considered throughout the procedure, due to the patient being placed in a prolonged prone or concord position.

For surgical correction of kyphotic deformities, a three-column osteotomy through a posterior approach is usually performed over the C7 level for better C2-C7 SVA and CBVA correction. Anatomically, the vertebral artery (VA) usually enters the transverse foramen at C6. Selecting C7 as the osteotomy level not only avoids injury to the VA but also could be beneficial due to a wider spinal canal and sparing of upper extremity function in case of spinal cord injury [22].

During the operation, wide exploration of the cervicothoracic junction is first done following insertion of screws. While lateral mass screws may be used in correction surgery, it is better to use both cervical and thoracic pedicle screws for their stronger pullout strength. A construct at least three levels above and below the osteotomy site is suggested due to general osteoporosis and the long auto-fused AS spine. O-arm navigation can be very helpful, especially as anatomical landmarks are often difficult to identify.

The posterior osteotomy is first done with a C7 laminectomy and bilateral C6-T1 facetectomy. The anterior column osteotomy can be done either using a pedicle subtraction osteotomy (PSO) or Smith-Peterson osteotomy (SPO). Once all three-column osteotomies are done, the rods can be contoured with the desired configuration, and thoracic nuts are tightened. The patient's head, which remains fixed to the Mayfield system, can be unlocked and adjusted to a more extended position gradually, and kyphosis can be corrected until satisfied positioning is reached. Neuromonitoring, especially motor evoke potential (MEP), should be closely monitored, as translation injury, cord compression from the osseous component, or excessive dura impingement may occur at this stage of correction.

Several osteotomy techniques are mentioned throughout current literature. SPO was first adapted to treat cervical kyphosis patients by Mason et al. [24] and Urist et al. [25] in the 1950s. With the SPO technique came the advantage of larger degrees of correction with less posterior element and spinal canal shortening. Some authors suggested an additional anterior approach osteotomy prior to the SPO procedure for anterior release [22]. Recently, Maciejczak et al. [26] reported a case of the modified SPO procedure using a crosswise osteotomy over the pedicles, reaching the anterior vertebral body to prevent aberrant osteoclasis. A downside to the technique is that it is very technically demanding.

All corrective surgeries for AS kyphotic deformities are very challenging. Complications may include spinal cord injury, C8 root injury during osteotomy, or

neural foramen stenosis after correction. Other complications include postoperative dysphagia, or nonunion with pseudarthrosis [22].

Navigation Technology for the Surgical Treatment of Ankylosing Spondylitis

There is a scarcity of studies investigating the application of navigation technologies for surgical treatment in AS cases. Screw placement can be challenging in AS patients due to distorted anatomy. Guided imaging technology provides real-time orientation and device implant accuracy, which may decrease postoperative complications and/or failed surgeries in AS cervical spine cases. A study demonstrated that surgical treatment of cervical spine fractures in AS patients via posterior stabilization using CT scanner-based navigation intraoperatively resulted in a 4.5% inadequate anatomical insertion rate. Neither screw malposition nor any other intraoperative events were complicated by any neural, vascular, or visceral injury, and follow-up indicated complete bone fusion of the anterior part of the spinal column and lateral masses at one year follow-up. CT-guided posterior cervical stabilization may be a reliable and safe method for addressing C-spine complications and fractures among AS patients [27]. However, the use of navigation technology in AS cases requires more studies and evidence.

Nanomedicine: A Novel Treatment

Recent advancements in the realm of nanomedicine allow for longer drug retention at the targeted delivery site. Although there is currently no standard nano-based drug therapy for AS, well-established nano-preparations, such as liposomes, polymeric nanoparticles, and hydrogels, have already been successfully incorporated in the treatment of other chronic inflammatory diseases, such as osteoarthritis, backache, and RA, and therefore show promise in being a potential alternative in treating AS [28].

Liposomes, which are normally prepared using biodegradable nontoxic lipids, have the ability to hold both hydrophilic and hydrophobic drugs. Liposomal nanopreparations also increase the half-life and retention time of certain liposome-based NSAIDs, such as indomethacin, ibuprofen, etc., which have already been successfully used in the treatments of RA and osteoarthritis. Elron-Gross et al. reported improved retention time of diclofenac after using collagen lipid conjugates to encapsulate the drug, which allowed for slow release in the synovial area [28]. In a more recent example, Rakeshchandra et al. synthesized a peptide ligand ART-1 and encapsulated it in an IL-27-coated liposome (ART-1-IL-27). These nano-prepared

liposomes not only displayed significant binding to endothelial cells but also were better able to hone in on arthritic joints when compared to control liposomes in Lewis rat models [29].

Polymeric nanoparticles are prepared using chitosan, poly-lactic acid (PLA), poly-lactic glycolic acid (PLGA), among many others. These particles increase the clinical efficacy of certain NSAID medications like diclofenac, which are well tolerated by patients but have unnecessarily high dosage frequencies when compared to other common NSAIDs, like naproxen, ibuprofen, sulindac, and diflunisal. The use of a slow-release PLGA microparticle containing diclofenac by Tuncay et al. in the treatment of osteoarthritis, for example, has been shown to effectively reduce dosing frequency [30]. In another report, the successful delivery of leukemia inhibitory factors (LIF) conducted by Stephanie et al. utilized fabricated poly(ethylene glycol)-poly(lactic acid) (PEG-PLA) polymer backbone polymeric nanoparticles (NanoLIF), with modified CD-11b antibody surfaces to target peripheral macrophages, and significantly decreased inflammation by inhibiting M1-cell growth over 72 h [31].

AI and Technological Modeling

As first-line agents, nonsteroidal anti-inflammatory drugs (NSAIDS) are initially prescribed to AS patients; however, studies indicate that over 40% of them exhibit NSAID nonresponse. For these nonresponders, second-line drugs such as TNF inhibitors may be prescribed, but guidelines require trials of at least two NSAIDS for at least 3 months, causing delays in effective treatment.

Artificial neural networks (ANN) are modern machine learning models that aim to identify, analyze, and assign early anti-TNF user candidacy with better precision and diagnostic ability than conventional statistical models. The study by Samsung Health Center employed computer models that used demographic (age, sex, height, weight, HLA-B27 status) and laboratory data (white blood cell count, hemoglobin, platelet count, blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST), alanine transaminase (ALT), ESR, and CRP) as baseline characteristics to train an ANN for predicting early TNFi candidate populations. By enrolling AS candidates in both early TNF and non-early TNF user groups, researchers constructed a clinical dataset matrix, which was used to construct the model architecture for the ANN 5 hidden layers and 60 hidden nodes per layer. The ANN model was then trained to predict TNFi user candidacy by combining the data into hyperparameters and then tested against the conventional logistic regression model along with SVM, RF, and XGBoost machine models. The study's ANN model more accurately predicted symptom progression, anti-TNF receptivity, and treatment appropriateness for these AS patients than any of the other models. Results of this ANN model indicates the possibility of training precise machine models using only laboratory data and demographic data recorded in an average clinical setting. Future AI

and ANN machine learning model studies should explore expanded parameters from wider datasets beyond a single hospital system [32].

References

1. Zhu W, He X, Cheng K, et al. Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res. 2019;7:22.
2. Britto NMF, Renor BS, Ghizoni E, Tedeschi H, Joaquim AF. Spine surgery in patients with ankylosing spondylitis. Rev Assoc Med Bras (1992). 2018;64(4):379–83.
3. Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial Spondyloarthritis. N Engl J Med. 2016;374(26):2563–74.
4. Brewerton DA, Hart FD, Nicholls A, Caffrey M, James DC, Sturrock RD. Ankylosing spondylitis and HL-A 27. Lancet. 1973;1(7809):904–7.
5. Reveille JD. An update on the contribution of the MHC to AS susceptibility. Clin Rheumatol. 2014;33(6):749–57.
6. Reveille JD. The genetic basis of spondyloarthritis. Ann Rheum Dis. 2011;70(Suppl 1):i44–50.
7. Reveille JD, Witter JP, Weisman MH. Prevalence of axial spondylarthritis in the United States: estimates from a cross-sectional survey. Arthritis Care Res (Hoboken). 2012;64(6):905–10.
8. Julian-Santiago F, Garcia-Garcia C, Garcia-Olivera I, Goycochea-Robles MV, Pelaez-Ballestas I. Epidemiology of rheumatic diseases in Mixtec and Chontal indigenous communities in Mexico: a cross-sectional community-based study. Clin Rheumatol. 2016;35(Suppl 1):35–42.
9. Zeng SY, Gong Y, Zhang YP, et al. Changes in the prevalence of rheumatic diseases in Shantou, China, in the past three decades: a COPCORD study. PLoS One. 2015;10(9):e0138492.
10. Montoya J, Matta NB, Suchon P, et al. Patients with ankylosing spondylitis have been breast fed less often than healthy controls: a case-control retrospective study. Ann Rheum Dis. 2016;75(5):879–82.
11. Maas F, Spoorenberg A, Brouwer E, et al. Radiographic damage and progression of the cervical spine in ankylosing spondylitis patients treated with TNF-alpha inhibitors: facet joints vs. vertebral bodies. Semin Arthritis Rheum. 2017;46(5):562–8.
12. Davis JC Jr. Understanding the role of tumor necrosis factor inhibition in ankylosing spondylitis. Semin Arthritis Rheum. 2005;34(4):668–77.
13. Lee HS, Kim TH, Yun HR, et al. Radiologic changes of cervical spine in ankylosing spondylitis. Clin Rheumatol. 2001;20(4):262–6.
14. Lukasiewicz AM, Bohl DD, Varthi AG, et al. Spinal fracture in patients with ankylosing spondylitis: cohort definition, distribution of injuries, and hospital outcomes. Spine (Phila Pa 1976). 2016;41(3):191–6.
15. Chaudhary SB, Hullinger H, Vives MJ. Management of acute spinal fractures in ankylosing spondylitis. ISRN Rheumatol. 2011;2011:150484.
16. Werner BC, Samartzis D, Shen FH. Spinal fractures in patients with ankylosing spondylitis: etiology, diagnosis, and management. J Am Acad Orthop Surg. 2016;24(4):241–9.
17. Westerveld LA, Verlaan JJ, Oner FC. Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications. Eur Spine J. 2009;18(2):145–56.
18. Kurucan E, Bernstein DN, Mesfin A. Surgical management of spinal fractures in ankylosing spondylitis. J Spine Surg. 2018;4(3):501–8.
19. Vonhoff CR, Scandrett K, Al-Khawaja D. Minor trauma in ankylosing spondylitis causing combined cervical spine fracture and esophageal injury. World Neurosurg. 2018;119:151–4.
20. Kanter AS, Wang MY, Mummaneni PV. A treatment algorithm for the management of cervical spine fractures and deformity in patients with ankylosing spondylitis. Neurosurg Focus. 2008;24(1):E11.

21. Lazennec JY, d'Astorg H, Rousseau MA. Cervical spine surgery in ankylosing spondylitis: review and current concept. Orthop Traumatol Surg Res. 2015;101(4):507–13.
22. Hoh DJ, Khoueir P, Wang MY. Management of cervical deformity in ankylosing spondylitis. Neurosurg Focus. 2008;24(1):E9.
23. Song K, Su X, Zhang Y, et al. Optimal chin-brow vertical angle for sagittal visual fields in ankylosing spondylitis kyphosis. Eur Spine J. 2016;25(8):2596–604.
24. Mason C, Cozen L, Adelstein L. Surgical correction of flexion deformity of the cervical spine. Calif Med. 1953;79(3):244–6.
25. Urist MR. Osteotomy of the cervical spine; report of a case of ankylosing rheumatoid spondylitis. J Bone Joint Surg Am. 1958;40-A(4):833–43.
26. Maciejczak A, Wolan-Nieroda A, Guzik A. C7 extension crosswise osteotomy: a novel osteotomy for correction of chin-on-chest deformity in a patient with ankylosing spondylitis. J Neurosurg Spine. 2020:1–6.
27. Barsa P, Frohlich R, Adamik J, Suchomel P. Surgical treatment of cervical spine fractures in ankylosing spondylitis patients: posterior stabilization using intraoperative CT scanner-based navigation. Rozhl Chir. 2020;99(5):212–8.
28. Chevalier X. Intraarticular treatments for osteoarthritis: new perspectives. Curr Drug Targets. 2010;11(5):546–60.
29. Meka RR, Venkatesha SH, Moudgil KD. Peptide-directed liposomal delivery improves the therapeutic index of an immunomodulatory cytokine in controlling autoimmune arthritis. J Control Release. 2018;286:279–88.
30. Tuncay M, Calis S, Kas HS, Ercan MT, Peksoy I, Hincal AA. Diclofenac sodium incorporated PLGA (50:50) microspheres: formulation considerations and in vitro/in vivo evaluation. Int J Pharm. 2000;195(1–2):179–88.
31. Davis SM, Reichel D, Bae Y, Pennypacker KR. Leukemia inhibitory factor-loaded nanoparticles with enhanced cytokine metabolic stability and anti-inflammatory activity. Pharm Res. 2018;35(1):6.
32. Lee S, Eun Y, Kim H, Cha HS, Koh EM, Lee J. Machine learning to predict early TNF inhibitor users in patients with ankylosing spondylitis. Sci Rep. 2020;10(1):20299.