A Comprehensive Institutional Overview of Intrathecal Nusinersen Injections for Spinal Muscular Atrophy

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Abstract.
Background: Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder resulting in progressive muscle weakness. In December 2016, the U.S. Food and Drug Administration approved the first ever treatment for SMA, a drug named nusinersen (Spinraza) which is administered intrathecally. However, many SMA patients have neuromuscular scoliosis and/or spinal instrumentation resulting in challenging intrathecal access. Therefore alternative routes must be considered in these complex patients.

Methods: This study was reviewed and approved by our institution's institutional review board. From March to December 2017, institutional SMA patients were referred for intrathecal nusinersen injections. In select patients with spinal hardware, spinal imaging was requested to facilitate pre-procedure planning. Standard equipment for intrathecal injections was utilized. All patients were followed-up by their referring neurologist.

Results: A total of 104 intrathecal nusinersen injections were performed in 26 patients with 100% technical success. 60 procedures were performed without pre-procedural imaging and via standard interspinous technique. The remaining 44 procedures were performed in 11 complex (i.e. neuromuscular scoliosis and/or spinal instrumentation) patients requiring pre-procedural imaging for planning purposes. 19 of 44 complex procedures were performed via standard interspinous technique from L2 to S1. 22 of 44 complex procedures were performed using a neural-foraminal approach from L3 - L5. 3 of 44 complex procedures were performed via cervical puncture technique. There were no immediate or long-term complications but 1 short term complication of meningismus and back pain at the injection site.

Conclusion: Although we achieved 100% technical success in intrathecal nusinersen administration, our practice habits evolved during the course of this study. Our early experience has led to the development of an algorithm to assist in promoting safe and effective nusinersen administration in children with Spinal Muscular Atrophy regardless of SMA type, abnormal spinal anatomies and complex spinal instrumentation.

Keywords: Cervical puncture; Children; Neural-foraminal lumbar approach; Nusinersen; Spinal muscular atrophy; Spinraza.

Background.
Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder resulting in progressive muscle weakness (1). It is estimated to affect 1 in 10,000 live births (2). SMA is caused by a defect in the survival motor neuron (*SMN1*) gene at the end of exon 7 on chromosome 5 (3).
SMA is subdivided into 5 different groups from 0 to 4. SMA 4 is the adult onset of the disorder while 0 to 3 are the pediatric disorder subgroups. SMA type 0 is a prenatal disorder, with a lifespan of less than 6 months, characterized by severe neonatal hypotonia and early respiratory failure. SMA type 1 (Werdnig-Hoffman disease) affects more than 50% of all SMA patients and presents within the first 6 months of life. SMA 1 is characterized by the inability to sit unsupported, poor head control and variable suck and swallow difficulties. The life expectancy of these children is very short (less than 2 years) due to respiratory insufficiency and bulbar weakness. SMA type 2 (Dubowitz disease) has an onset between 6 and 18 months. These patients develop muscle weakness but can sit on their own. SMA type 3 (Kugelberg-Welander disease) has an onset between 18 months to 30 years of age. Patients with SMA 3 learn to walk but may lose the ability to walk over time. 70% of SMA 2 and 3 patients are alive at age 25 (4,5,6).
In December 2016, the U.S. Food and Drug Administration approved the first ever treatment for SMA, a drug named called nusinersen (Spinraza) (7). Nusinersen is antisense oligonucleotide that binds to *SMN2*, a paralogous gene to *SMN1*, promoting inclusion of exon 7. Increased exon 7 inclusion results in increased *SMN* production. Significant increases in Hammersmith Functional Motor scores (HFMSE) were reported in children with SMA who received this drug (8).
Nusinersen is administered intrathecally by standard lumbar puncture, typically performed with the patient under anesthesia with no significant complications reported (9). However, many SMA patients have neuromuscular scoliosis secondary to the disease, often treated surgically with spinal instrumentation and osseous fusion of the posterior spinal elements. As a result, standard lumbar punctures can be difficult to perform in this subset of patients (10). Therefore, alternative routes of access to the subarachnoid space, including neural-foraminal and cervical punctures, must be considered to effectively administer nusinersen in these complex patients.

Methods.
This retrospective study was approved by the institutional review board with a waiver of informed consent. From March 1, 2017 to December 31, 2017, all candidate SMA type 1, 2 and 3 patients seen by the Neurology service at our institution were referred to the Interventional Radiology department for intrathecal nusinersen injections. Both inpatients and outpatients were included as well as patients who had previously received nusinersen treatment at outside institutions. Patients with SMA 1 were scheduled for injection without the request of pre-procedural imaging. For patients with SMA 2 and 3, all previous imaging ordered for other medical indications, including chest, abdomen, spine, and scoliosis films, were reviewed. In select complex patients with spinal hardware and fusion of the posterior vertebral elements, lumbar spine CT, cervical spine CT and/or cervical spine MR were performed to facilitate pre-procedure planning.

All procedures were performed in the interventional radiology suite by 4 attending interventional radiologists and a single interventional radiology fellow under direct supervision from staff.

Cases were performed using either general anesthesia or with local anesthesia only. Two types of imaging guidance were utilized for needle placement, fluoroscopy and cone beam CT. The choice of imaging depended on patient body habitus, history of spinal hardware, presence of posterior element osseous fusion, and planned route of intrathecal administration. If feasible, no imaging guidance was utilized for standard interspinous lumbar puncture, as per ALARA guidelines. Standard equipment for intrathecal injections included 1.5", 3.5", 5" and 7" 22-gauge spinal needles. Routes for injection included standard interspinous lumbar punctures, neural-foraminal lumbar punctures, and cervical punctures (C1-C2 and occiput-C1 punctures). For a standard interspinous lumbar puncture, positioning of patient was exclusively left lateral decubitus. For neural-foraminal lumbar punctures, either prone or lateral decubitus positioning was used. For cervical punctures, only left lateral decubitus position was used.

Confirmation of subarachnoid space needle tip position was confirmed with spontaneous return of CSF. If there was no spontaneous return despite correct needle tip position confirmed with fluoroscopic orthogonal views, < 1 mL of Isovue M-200 was injected for confirmation. After collection of 5 mL of CSF per protocol, 12 mg (5 mL) of nusinersen were slowly injected intrathecally over 1-2 minutes. The spinal needle was then withdrawn, and a sterile dressing was placed.

For procedures performed with general anesthesia, patients were sent to the recovery room and were discharged home once criteria were met. Patients receiving local anesthetic only were immediately discharged home or sent back to their ward. All patients were followed-up by their referring neurologist.

Procedures were performed at prescribed treatment intervals with the second and third doses being administered 2 weeks following the previous dose. The 4th dose was scheduled a month after the 3rd dose and the 5th dose scheduled 4 months after the 4th dose.

Results.

A total of 104 intrathecal nusinersen injections were performed in 26 children (9 boys, 17 girls) with 100% technical success. Of the 26 children, 9 were diagnosed with SMA type 1, 14 with SMA type 2, and 3 with SMA type 3. Children ranged in age from 4 months to 218 months (mean of 93.5 months) with weighed 5.4 kg to 78 kg (mean of 25.7 kg).

Sixty procedures were performed in 15 children (9 with SMA type 1, 5 with SMA type 2 and 1 with SMA type 3) without the need for pre-procedural imaging and via standard interspinous technique at L2-L3 or L3-L4 positioned in left lateral decubitus using 1.5" or 3" spinal needles. Twelve children (47 procedures) were injected under general anesthesia and 3 children (13 procedures) were injected using only local anesthesia. Forty-one injections were performed without imaging guidance and the remaining 19 were performed with fluoroscopic guidance (fluoroscopy time range of 0.1 min to 1.9 min; Fig. 1). Total procedure times, defined as the time from when the child entered the interventional radiology suite to when the child exited the interventional radiology suite, ranged from 14 min to 66 min (mean of 28.1 min).

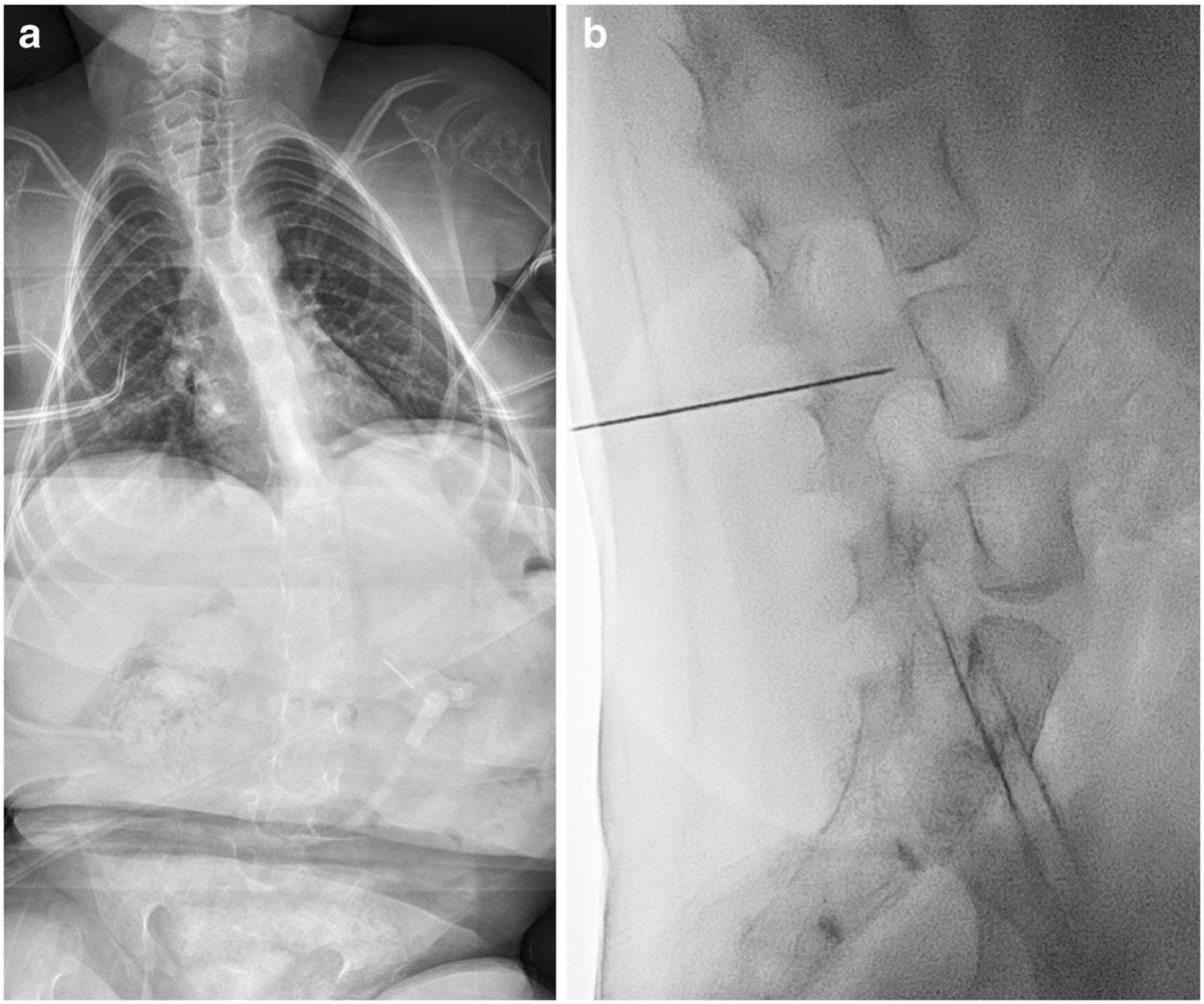

Figure 1: Spinal muscular atrophy type 2 in an 8-year-old boy. **a** Anteroposterior diagnostic radiograph demonstrates thoracolumbar scoliosis and neuromuscular disease. **b** Lateral fluoroscopic image demonstrates spinal needle tip positioned in the subarachnoid space at L3-L4 via an interspinous approach. Note true lateral projection using vertebral bodies and neural foramina as internal landmarks

The remaining 44 procedures, performed in 11 children (9 with SMA type 2 and 2 with SMA type 3), were more complex (i.e. spinal hardware +/- osseous fusion) and required preprocedural imaging for planning purposes. In chronological order, the first three complex patients underwent diagnostic imaging in which a CT scan of the lumbar spine was obtained to ascertain potential intrathecal access at various lumbar levels. These children also had synchronous cervical spine CT performed for alternative intrathecal access via C1-C2 or occiputC1 puncture if necessary. The next three complex patients had the same pre-procedural imaging performed with the addition of an MR cervical spine to aid potential cervical puncture. The following three children, seen in late 2017, had CT lumbar spine and MR cervical spine without CT cervical spine. The last two complex patients had only CT lumbar spine imaging. All pre-procedural imaging was performed without sedation or anesthesia. No child was denied therapy based on imaging findings.

Nineteen of these 44 procedures were performed in 5 children with pre-procedural imaging and via standard interspinous technique from L2 to S1, positioned in left lateral decubitus using 1.5”, 3.5” or 5” spinal needles (Fig. 2). Eleven injections were performed under general anesthesia and eight were performed with only local anesthesia. Seventeen injections were performed with fluoroscopic guidance (fluoroscopy time 0.5–5.0 min) and two without imaging guidance. Total procedure times ranged 21–88 min (mean of 38.0 min).

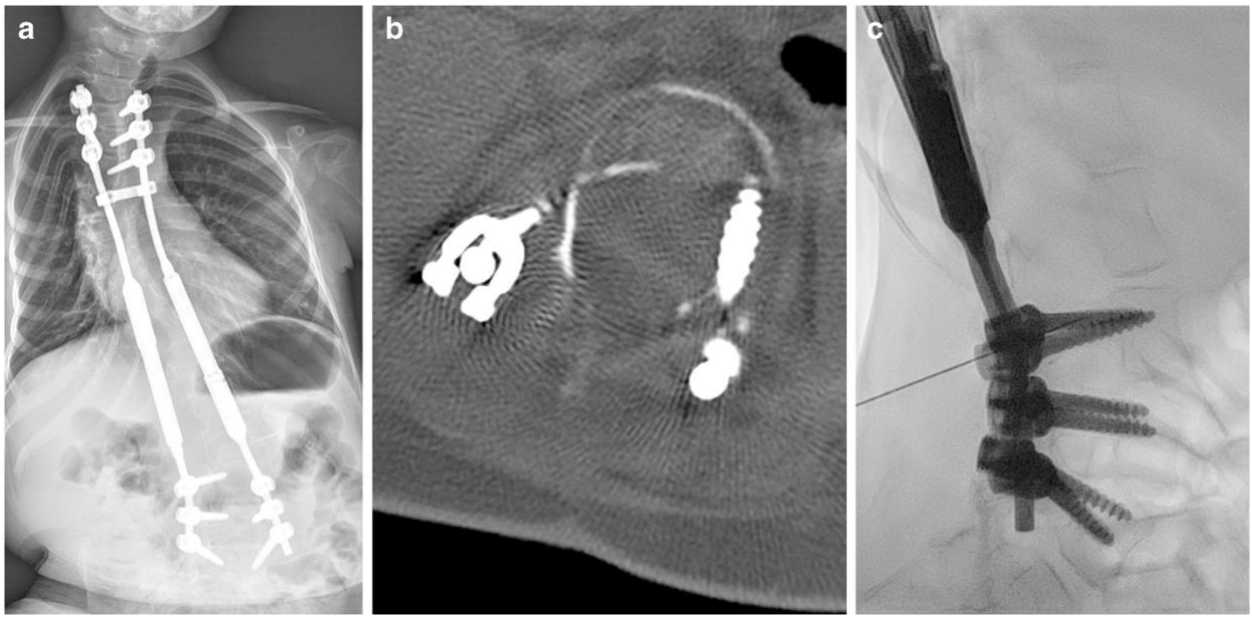

Figure 2: Spinal muscular atrophy type 2 and spinal hardware in a 7-year-old girl. **a** Anteroposterior radiograph demonstrates scoliosis post repair and neuromuscular disease. **b** Axial image from pre-procedural non-contrast diagnostic lumbar spine CT demonstrates patency of the posterior spinal canal, with lack of bony fusion, at the level of the most cephalad transpedicular screws. **c** Lateral fluoroscopic image demonstrates spinal needle tip superimposed over the most cephalad transpedicular screws, positioned in the subarachnoid space at L2-L3 via an interspinous approach. Again, note true lateral projection using vertebral bodies and neural foramina as internal landmarks at the level of interest

Twenty-two of the 44 procedures were performed in 7 children with pre-procedural imaging using a neural-foraminal approach from L3 to L5, all under general anesthesia. The first three procedures in chronological order were injected using XperCT (Philips Allura Xper FD System) for localization and XperGuide (Philips), a 3-D guidance system utilizing fluoroscopy overlay, for needle guidance (Fig. 3). These children were positioned prone using 5” and 7” spinal needles for intrathecal access. The fluoroscopic time ranged from 3.0 min to 5.5 min and the procedure time ranged from 65 min to 89 min (mean of 80.3 min). The next 19 procedures were positioned in lateral decubitus position and injected exclusively using fluoroscopic guidance (times 0.9 min to 3.6 min) using 5” and 7” spinal needles (Fig. 4). The procedure time ranged 27–65 min (mean of 41.2 min).

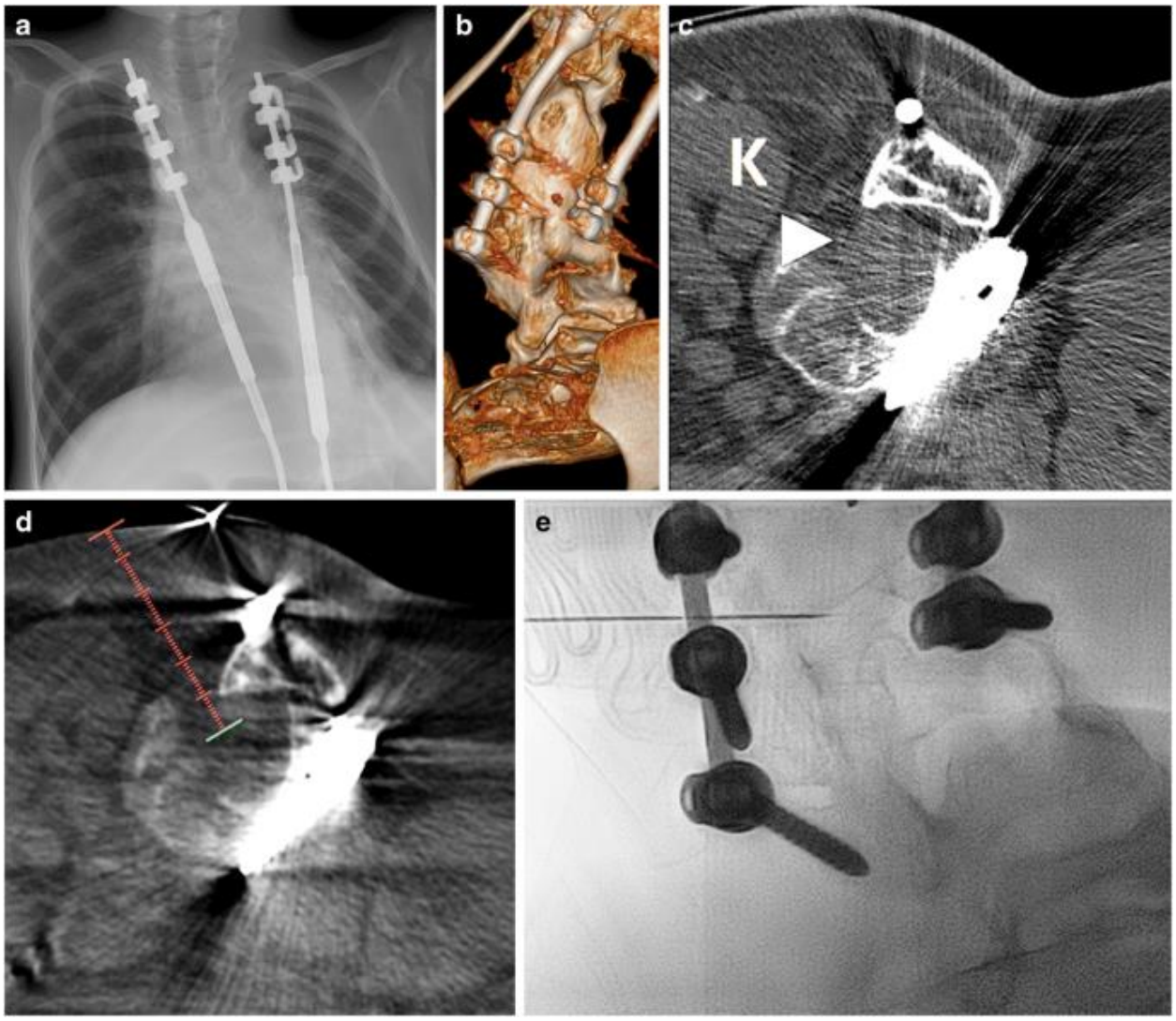

Figure 3: Spinal muscular atrophy type 2 and rod insertion in a 10-year-old boy. **a** Anteroposterior radiograph demonstrates thoracolumbar scoliosis with spinal rods. **b** Three-dimensional reconstruction from source non-contrast diagnostic lumbar spine CT images demonstrates diffuse bony fusion of the lumbar posterior elements, prohibiting interspinous access. **c** Axial image from the non-contrast diagnostic lumbar spine CT demonstrates plausible spinal canal access via a patent left L2-L3 neural foramen (*arrowhead*). Note needle access route immediately medial to the left kidney (*K*). **d** XperCT axial image at the level of the left L2-L3 neural foramen with superimposed needle planning into the subarachnoid space via XperGuide. **e** Fluoroscopic overlay using XperGuide confirms midline needle tip position within the thecal sac at L2-L3

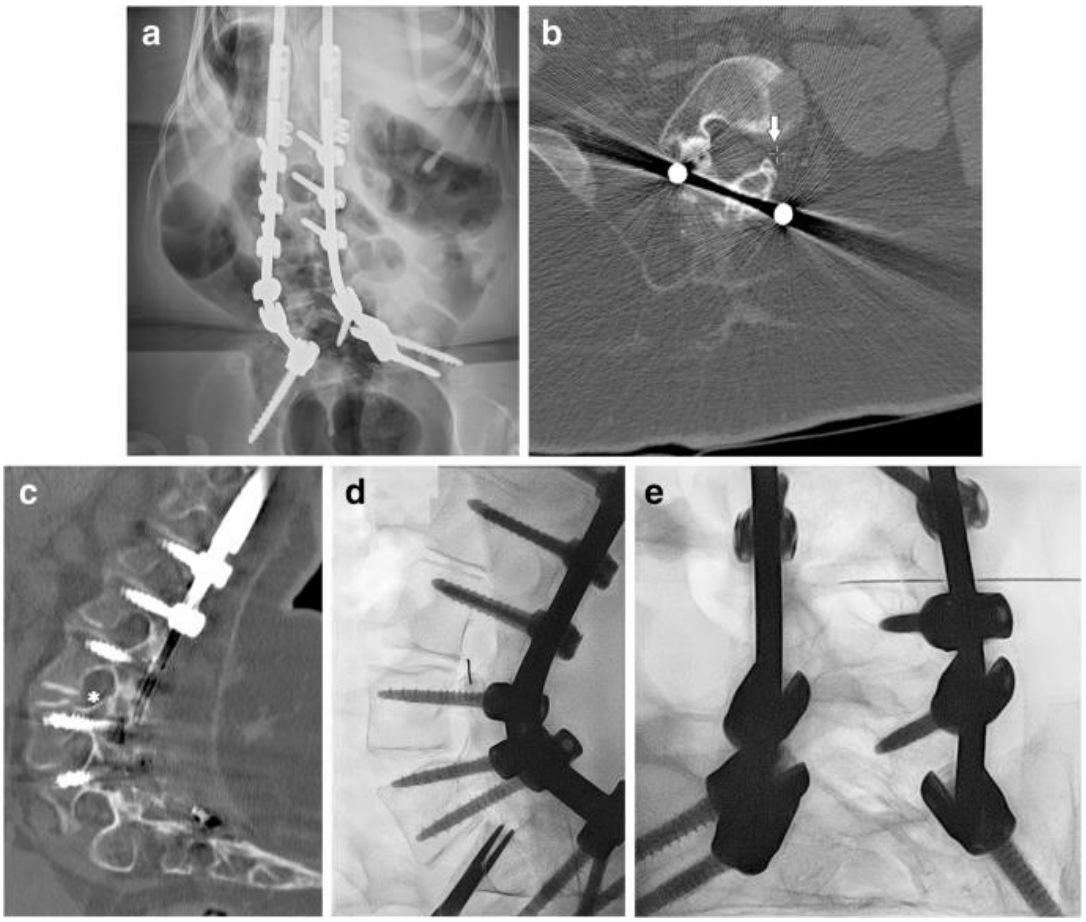

Figure 4: Spinal muscular atrophy type 2 post spinal fusion and rod placement in a 14-year-old girl. **a** Anteroposterior lumbar spine radiograph demonstrates spinal fusion hardware. **b, c** Axial and sagittal non-contrast lumbar spine CT images demonstrate plausible intra-thecal access via the left L3-L4 neural foramen (*arrow*). Note positioning of the in the lower half of the neural foramen (*asterisk*) to avoid injury to the neurovascular structures. **d, e** Lateral and anteroposterior fluoroscopic images demonstrate spinal needle traversing the lower neural foramen with tip positioned in the central canal

Three of the 44 procedures were performed in 2 children with pre-procedural imaging and via cervical puncture technique. All children were positioned in left lateral decubitus and under general anesthesia using 3.5” 22-gauge spinal needles. Two procedures were performed via a C1-C2 puncture utilizing fluoroscopic guidance (fluoroscopy times of 4.9 min and 4.9 min; Fig. 5). The procedure times were 65 min and 75 min (mean of 70 min). One procedure was performed at occiput-C1 utilizing fluoroscopic guidance (time 14.5 min; Fig. 6). The procedure time was 87 min.

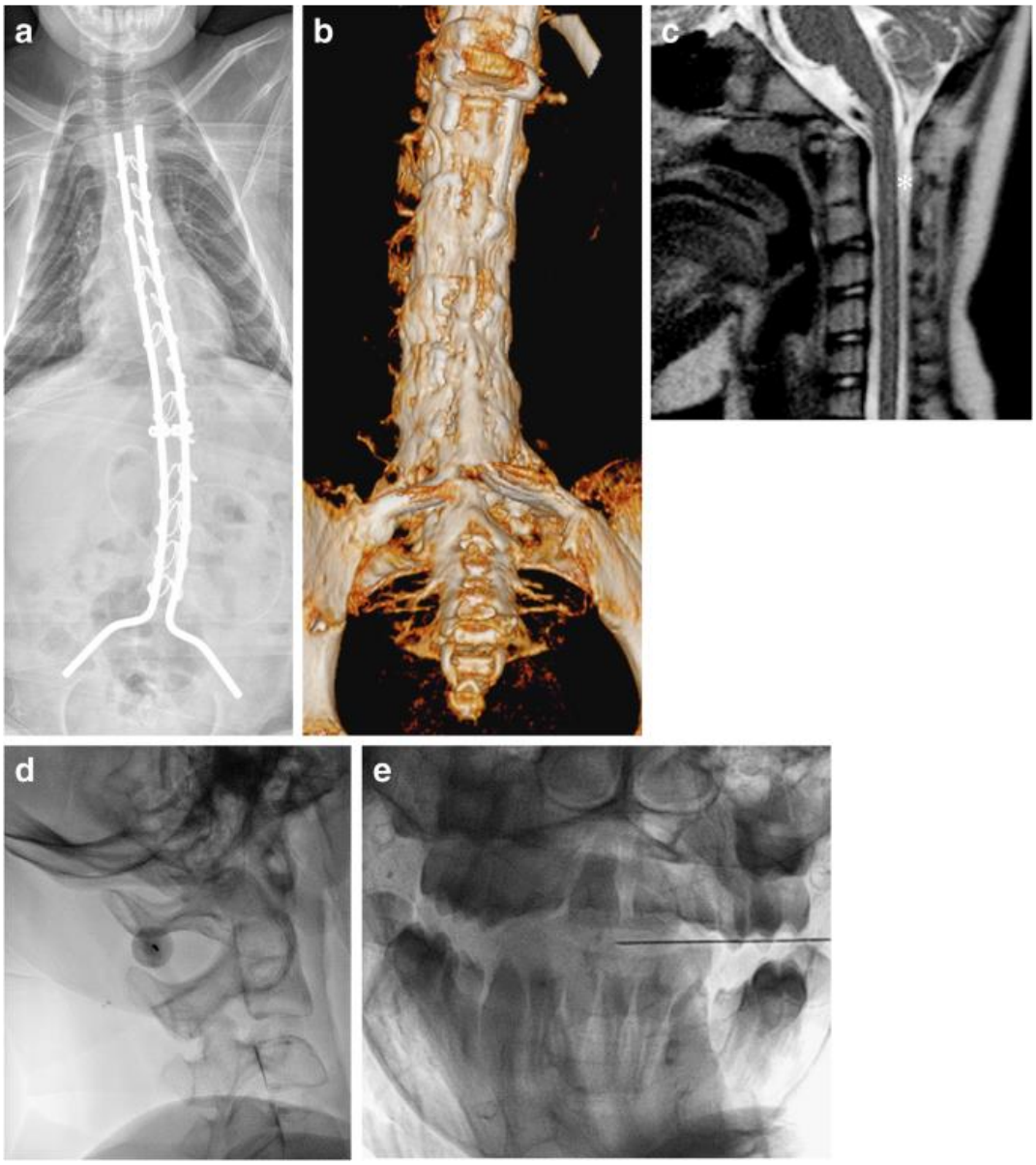

Figure 5: Spinal muscular atrophy type 3 with spinal fusion in a 14-year-old boy. **a** Anteroposterior thoracolumbar radiograph demonstrates extensive spinal fusion hardware. **b** Three-dimensional reconstruction from source non-contrast diagnostic lumbar spine CT images demonstrates diffuse bony fusion of the entire lumbar posterior elements. **c** Sagittal T2-weighted cervical MR clearly demonstrates the cerebrospinal fluid space (*asterisk*) posterior to the spinal cord for cervical puncture. **d, e** With the boy in lateral decubitus position, lateral fluoroscopic image demonstrates the spinal needle superimposed over the C1-C2 interspace. The orthogonal view is used for monitoring progress of the needle tip position to midline

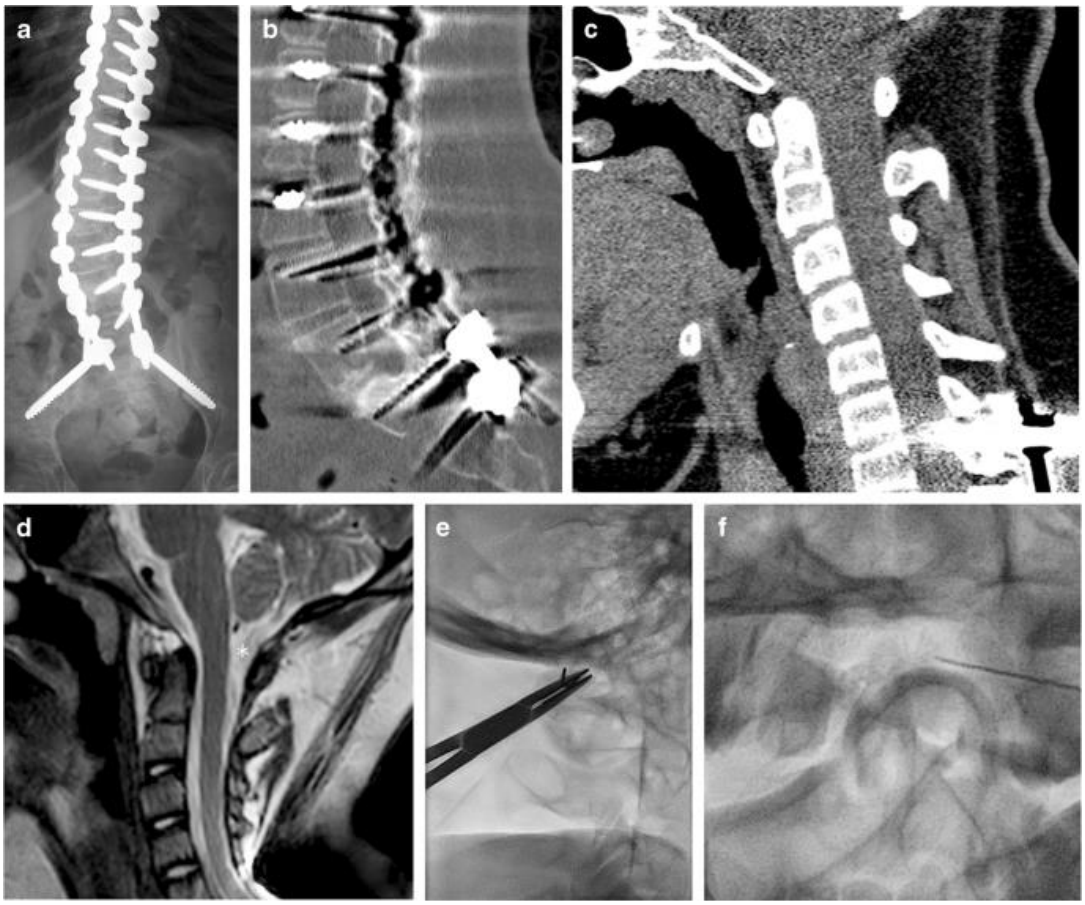

Figure 6: Spinal muscular atrophy type 2 post spine stabilization in a 13-year-old girl. **a** Anteroposterior lumbar radiograph demonstrates extensive spinal fusion hardware. **b** Sagittal diagnostic non-contrast lumbar spine CT image demonstrates diffuse bony fusion of the posterior elements, with streak artifact obscuring neural foraminal approach. **c** Sagittal diagnostic non-contrast cervical spine CT fails to precisely define the cerebrospinal fluid (CSF) space of the cervical spine despite soft-tissue windowing. **d** Sagittal T2-weighted cervical MR clearly demonstrates the CSF space (*asterisk*) posterior to the spinal cord for cervical puncture. **e, f** With the girl in lateral decubitus position, lateral fluoroscopic image demonstrates the spinal needle superimposed over the occiput-C1 interspace. The orthogonal view is used for monitoring progress of the needle tip position to midline

Of the 104 procedures, there were no immediate complications. There were two short-term complications in a single child who presented with meningismus and back pain at the injection site following each procedure. One of these episodes resulted in hospital admission. The child's symptoms improved with pain medications and the child was discharged. There are no reported long-term complications. All children enrolled in the program receive life-long follow-up by a pediatric neurologist. One child died 2 months after receiving a fourth dose as a result of cardiopulmonary arrest from unrelated causes.

Discussion.

In this study we successfully administered nusinersen intrathecally in all 104 procedures. Although we achieved 100% technical success, as the study progressed, our practices evolved.

For children with SMA type 1 or SMA types 2 or 3 without spinal hardware, a standard lumbar puncture technique can be used to administer nusinersen. For children with SMA type 1, imaging

guidance is generally not required because these children are younger than 1 year, with little to no spinal deformity, and a standard lumbar puncture can be performed. In children with SMA types 2 and 3 where fluoroscopy is necessary for needle guidance, a rotating C-arm is preferred. In our experience, even when children with SMA types 2 and 3 did not have spinal hardware or osseous fusions, they frequently had significant scoliosis and abnormal spinal anatomy requiring the use of rotating fluoroscopy to obtain a true lateral or anteroposterior fluoroscopic image of the lumbar spine. Although all of these children were placed in a left lateral decubitus position, the C-arm was frequently rotated to obtain true anteroposterior and lateral projections to guide needle placement. Therefore the use of a stationary C-arm would be less effective, potentially decreasing technical success and increasing radiation dose from higher fluoroscopy times.

Children with SMA types 2 and 3 with spinal hardware and fusions proved to be more challenging when planning nusinersen administration. These children all received non-contrast CT of the lumbar spine to ascertain potential lumbar intrathecal access. For those children in whom a lumbar interspinous approach was achievable, fluoroscopy was consistently utilized. Despite the procedural technique being identical to that in children without spinal hardware, our average procedure times increased from 28.1 min to 38.0 min. Potential causes of an increased average procedure time might be linked to the more severe neuromuscular deformity of the child, resulting in greater time to adequately position the child or to successfully obtain intrathecal access. The difficulty of performing a lumbar puncture in children with spinal hardware led to additional imaging being requested prior to the procedure. Initially, a CT of the cervical spine was requested in these children because of the possibility of failure of entry through the lumbar region. After review of the cervical spine CT, we realized there was difficulty identifying the cervical CSF despite adjusting our viewing window. Therefore we adjusted our practice and substituted a cervical MR for the cervical CT. This proved to be useful in three cases where entry via a lumbar interspinous approach was unsuccessful. Two cases were performed via a C1-C2 approach. The third cervical puncture was performed via an occiput-C1 approach because of the failure of access at C1-C2. Entry through the cervical region resulted in a significantly increased procedure time, averaging 75.6 min. The likely cause for the increased average procedure time is the failure of initial attempts to administer the dosage through the lumbar region.

As we continued to review pre-procedural non-contrast lumbar CTs in the children with SMA types 2 and 3 with spinal hardware and fusions, we attempted a lumbar neural-foraminal approach to avoid cervical punctures when interspinous lumbar approaches were either impossible or unsuccessful because of the child's pathological anatomy (i.e. scoliosis, asymmetrical osseous fusion; Fig. 4). A total of 22 neural-foraminal lumbar approaches were performed, with the first 3 using XperCT and XperGuide with the child in prone position. Although we achieved technical success, we quickly adjusted our practice because average procedural times were lengthy at 80.3 min and dose elevated with the use of CT. XperCT and XperGuide added no beneficial information over plain fluoroscopy. Therefore we performed the next 19 neural-foraminal approaches with a rotating C-arm only, allowing for us to position the child in lateral decubitus position contralateral to the accessible neural foramen and get a true lateral projection. Not only did this result in shorter procedural times (41.2 min vs. 80.3 min) and decreased fluoroscopic times (0.9–3.6 min vs. 3.0–5.5 min), but it also eliminated the need for prone positioning. Placing these children prone is more time-consuming because tracheal intubation is required. It is more challenging for the anesthesiologist and therefore leads to

longer procedural times for intubation and, second, for safe patient positioning as a result of their body habitus. In addition, children with SMA generally recover poorly from general anesthesia. This is heightened with prone positioning because atelectasis is increased. By not using a prone position, there was no prolonged post-anesthesia care.

Most important, our evolved approach of neural-foraminal access via fluoroscopic guidance in the lateral decubitus position with a rotating C-arm closely resembled our procedural times (41.2 min vs. 38.0 min) and fluoroscopic times (0.9–3.6 min vs. 0.5–5.0 min) from our initial approach of standard interspinous technique in complex patients with spinal hardware +/- osseous fusions. Also, after implementing the neural-foraminal approach, we performed no cervical punctures in the period studied. Accordingly, the final step in evolving our institutional practice was to completely cancel pre-procedural imaging of the cervical spine (CT and MR), with the only pre-procedural imaging being a non-contrast lumbar spine CT in children with spinal hardware +/- osseous fusions. In rare cases where a neural-foraminal approach is unsuccessful and cervical puncture is necessary, the child is called back for a cervical MR.

Conclusion.

Our early experience with nusinersen administration has led to the development of an algorithm (Fig. 7) to assist in promoting safe and effective nusinersen administration in children with spinal muscular atrophy regardless of SMA type, abnormal spinal anatomies and complex spinal instrumentation. Our 100% technical success of intra-thecal access suggests that more aggressive surgical approaches, such as reservoir placement or creation of a surgical window via a bone graft, should be reserved for children with no safe percutaneous access routes.

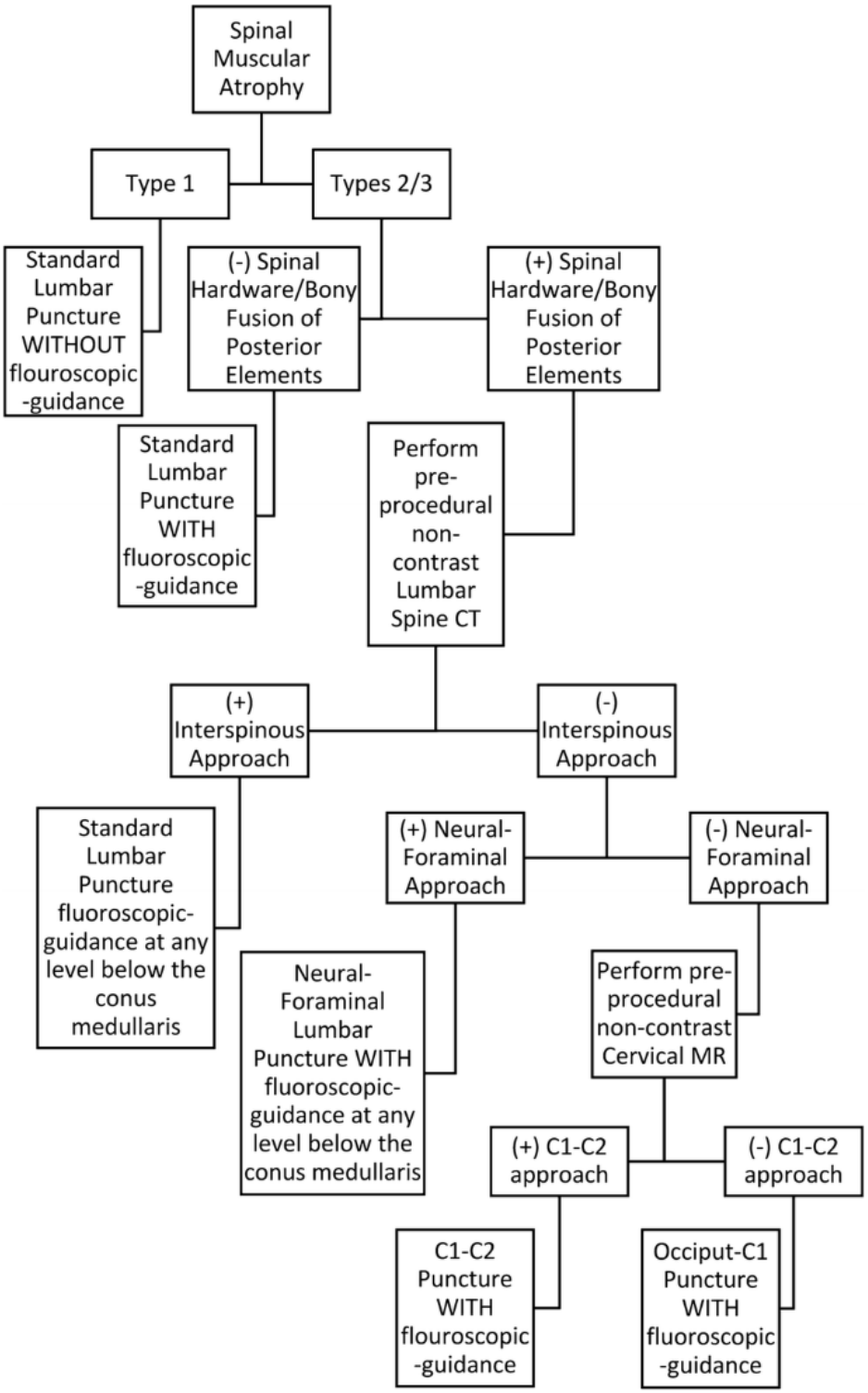

Figure 7:
Approach to intra-thecal therapy in children with spinal muscular atrophy (SMA). The approach to the child with SMA depends on the status of the bony spine. Children without scoliosis, spinal fusion or instrumentation (i.e. simple spine) are candidates for non-image-guided standard interspinous lumbar puncture. In contrast, children with a complex spine require pre-procedural imaging evaluation for route planning and in most cases intra-procedural image guidance

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