



Outcomes of Surgical Correction of Atlantoaxial Instability in Patients with Down Syndrome: Systematic Review and Meta-Analysis

Ryan C. Hofler¹, Nathan Pecoraro², G. Alexander Jones¹

BACKGROUND: Atlantoaxial instability (AAI) is a common cause of neurologic dysfunction and pain in patients with Down syndrome (DS), frequently requiring instrumented fusion of the upper cervical spine. Despite this, optimal treatment strategy is controversial.

METHODS: A systematic review of the literature was performed according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis statement to identify patients with AAI and DS were treated with upper cervical spine fusion. Patient demographics, preoperative symptoms, fixation type, and outcome measures including complications, neurologic outcomes, and bony fusion status were gathered for patients in the included publications. Meta-analysis was performed to compare outcomes of different types of fixation constructs.

RESULTS: Of the 1191 publications retrieved, 51 met inclusion criteria, yielding 137 patients. Six fixation strategies were identified: noninstrumented ($n = 6$), wiring ($n = 77$), wiring with rods ($n = 14$), screw fixation ($n = 33$), hook and rod fixation ($n = 2$), and screw and wire fixation ($n = 5$). Constructs with screws and rods had greater bony union ($P = 0.003$) and a lower rate of revision surgery ($P = 0.047$), loss of reduction or pseudoarthrosis ($P = 0.009$), halo utilization ($P < 0.001$), and early neurologic decline ($P = 0.004$) compared with wiring alone. Constructs with wires and rods had greater bony union ($P = 0.036$) than wiring alone.

CONCLUSIONS: Numerous fixation strategies exist for AAI in patients with DS. Using a combination of screws, rods, and wiring in appropriately selected patients may help reduce the high rate of surgical complications in these patients.

INTRODUCTION

Down syndrome (DS) is one of the most common genetic disorders in humans, affecting roughly 1 in 700 live births.¹ In addition to developmental delay, short stature, and distinct facial features, this condition is associated with numerous orthopedic conditions.²⁻⁹ Atlantoaxial instability (AAI), caused by ligamentous laxity, is a common cause of pain, torticollis, and neurologic dysfunction, affecting an estimated 12%–20% of patients with DS.^{7,10,11} Although surgical intervention with spinal cord decompression, deformity reduction, internal fixation, and fusion is often indicated to address AAI in patients with DS, it is often plagued by complications, poor neurologic outcomes, and need for revision surgery.^{4,12-15}

To date, numerous case reports and case series have been published on the surgical treatment of AAI in patients with DS, employing a number of fixation strategies. However, no randomized trials or meta-analyses have been performed to assess overall outcomes from treatment of AAI or compare the efficacy of different treatment strategies. In light of this paucity of literature despite the available data, the present study was undertaken to provide a thorough systematic review and meta-analysis of these surgical treatments.

Key words

- Atlantoaxial instability
- Down syndrome
- Meta-analysis
- PRISMA

Abbreviations and Acronyms

- AOI:** Atlanto-occipital instability
- AAI:** Atlantoaxial instability
- BMP:** Bone morphogenetic protein
- DS:** Down syndrome
- HRR:** Hook and rod fixation
- NIF:** Noninstrumented fusion
- SF:** Screw fixation
- SWF:** Screw and wire fixation

WOF: Wire-only fixation

WRF: Wire-and-rod fixation

From the ¹Department of Neurosurgery, Loyola University Medical Center, Maywood; and ²Stitch School of Medicine, Loyola University Chicago, Maywood, Illinois, USA

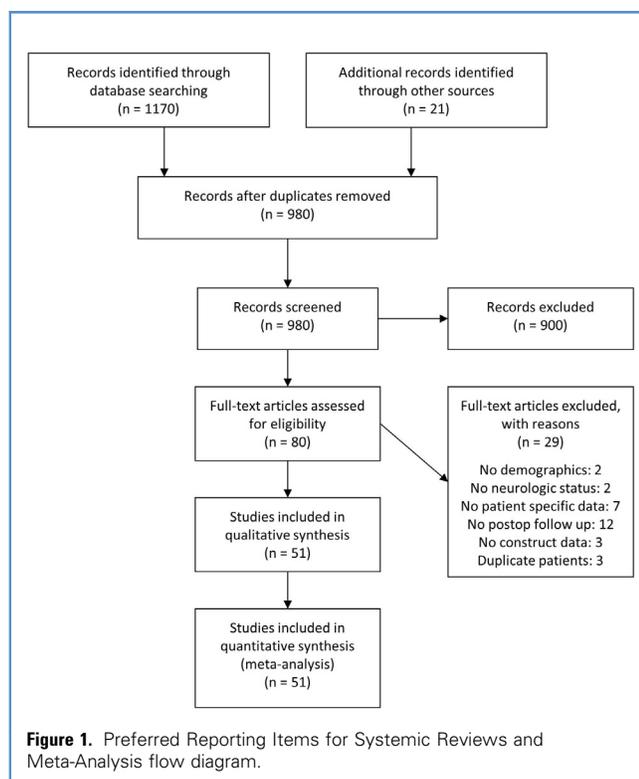
To whom correspondence should be addressed: G. Alexander Jones, M.D.
[E-mail: alexander.jones@lumc.edu]

Citation: *World Neurosurg.* (2019) 126:e125-e135.
<https://doi.org/10.1016/j.wneu.2019.01.267>

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

1878-8750/\$ - see front matter © 2019 Elsevier Inc. All rights reserved.



METHODS AND MATERIALS

Study Inclusion

A systematic search was performed in PubMed, Scopus, and the Cochrane Library. The last search was performed on 18 May, 2018 and went back as far as data were available. The PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analysis) statement was followed.¹⁰ References derived from the included studies were evaluated to find additional studies. The search of all fields was performed with the following string: ("down syndrome") AND (("cervical fusion") OR ("craniovertebral fusion") OR ("atlantoaxial" OR "atlanto-axial") AND ("fusion" OR "instability" OR "dislocation" OR "subluxation"))), yielding a total of 1170 records. Duplicate records were removed, and the rest were screened for inclusion by title and abstract review. Full-text article review was performed for any surgical case reports, case series, or trials pertaining to open fusion of the upper cervical spine for AAI in patients with Down syndrome.

Studies were included in the meta-analysis if they presented detailed and complete information on the patients involved. Articles were excluded if individual patient information was lacking for gender, age, preoperative diagnosis, neurologic function, surgical instrumentation used, follow-up neurologic status, or status of arthrodesis at last follow-up. Additional exclusion criteria included publications in languages other than English and follow-up <3 months. Patients from the included studies were compiled into a database for analysis if they had a diagnosis of DS and underwent open surgical fusion of the upper cervical spine.

Individual patients were subsequently excluded from analysis if they lacked preoperative, operative, or postoperative details; had follow-up <3 months; or had fusion extending to the thoracic spine. Patients presented in >1 manuscript were only included once in the database and were excluded from the articles with the shorter follow-up period.

Preoperative and Operative Data

Age, gender, preoperative neurologic status, presenting symptoms, and year of publication were identified for each patient included. Neurologic status was consolidated into normal or any degree of dysfunction. Other presenting symptoms included torticollis and neck pain. Operative details included type of instrumentation used, most rostral level instrumented (occiput or atlas), and postoperative immobilization device (halo, cervical collar, other orthosis, or none).

Noninstrumented fusion (NIF) was defined as open fusion without placement of internal hardware. Wire-only fixation (WOF) includes any open fusion using only wires or cables. Wire-and-rod fixation (WRF) denotes open fusion with wires or cables securing rigid rods to the spine. Screw fixation (SF) involves the use of screws, with or without connecting rods, and without wires or cables. Hook and rod fixation (HRF) was defined as fixation using hooks and connecting rods, without use of screws, wires, or cables. Screw-and-wire fixation (SWF) denotes fixation using screws and wires or cables, with or without connecting rods.

Certain data were not available for every patient but were recorded when available: timing of symptomatology (noted as acute, progressive, and/or transient); graft material used (autograft, allograft, bone morphogenetic protein [BMP]); and number of motion segments fused.

Outcome Measures

Outcome measures included need for revision surgery (including total number of revisions), bony union status at last follow up, complications, mortality, and neurologic outcome. The following were considered complications: loss of reduction, pseudoarthrosis, early neurologic deterioration (within 1 year of the index operation), late neurologic deterioration (greater than 1 year after the index operation), intracranial hemorrhage, postoperative radiculopathy, hardware failure, surgical site infection, cardiac event, respiratory failure, adjacent segment degeneration, cerebrospinal fluid leak, halo complications, deep venous thrombosis, urinary tract infection, pneumonia, and dysphagia. Neurologic outcome was graded as worse than preoperative examination, no change in preoperative deficit, partial improvement of preoperative deficit, and normal neurologic function.

Statistical Analysis

Patients were grouped by construct type into 1 of the 6 treatment groups defined earlier. Comparative statistics were performed to compare the preoperative, operative, and postoperative data for patients in the WOF, WRF, and SF groups. The group with wire or cable-only constructs (WOF) was used as the reference to individually compare the efficacy of the other 2 construct types (WRF and SF). For continuous variables including age, follow-up time, year of publication, and number of motion segments fused, a 2-sample t-test was employed. All other variables were analyzed as

Table 1. Included Studies as Identified by System Review of Literature

Author and Year	Number of Patients by Construct Type					
	Noninstrument	Wire or Cable Only	Wire and Rod	Screw and Rod	Hook and Rod	Screw and Wire
Dzenitis, 1966 ¹⁷		1				
Curtis et al., 1968 ¹⁸		2				
Finerman et al., 1976 ¹⁹		1				
Holmes et al., 1978 ²⁰		2				
Dawson et al., 1979 ²⁰		2				
Giblin et al., 1979 ²¹	1	1				
Nordt et al., 1981 ^{22,*}		1				
Shield et al., 1981 ²³		1				
Herring et al., 1982 ²⁴		1				
Sherk et al., 1982 ²⁵		1				
Koop et al., 1984 ²⁶		1				
Kobori et al., 1986 ²⁷		2				
Chaudhry et al., 1987 ^{28,*}		3				
Shikata et al., 1989 ¹⁵		8				
Segal et al., 1991 ^{14,†}	1	8				
Smith et al., 1991 ²⁹		3				
Briggs et al., 1992 ¹⁰		1				
Menezes et al., 1992 ^{30,*}		2				
Higo et al., 1995 ³¹			4			
Kohno et al., 1995 ³²					1	
Doyle et al., 1996 ¹²	2	13				
Hui et al., 1997 ³³		6				
Lowry et al., 1997 ³⁴		4				
Tseng et al., 1998 ³⁵		1				
Brockmeyer et al., 1999 ³⁶				5		
Pait et al., 1999 ^{37,‡}				1		
Cohen et al., 2001 ³⁸		1				
Parisini et al., 2003 ³⁹		1			1	
Masuda, et al., 2003 ⁴⁰				1		
Singh et al., 2003 ⁴¹				1		
Visocchi et al., 2003 ^{42,§}			1			
Yamazaki et al., 2004 ⁴³			1			
Nader-Sepahi et al., 2005 ¹³		8	1	3		
Reilly et al., 2006 ⁴⁴				1		2

*1 patient excluded for follow-up <3 months.

†1 patient excluded due to lack of atlantoaxial instability.

‡1 patient excluded due to lack of neurologic status.

§2 patients excluded due to duplication in another included study.

||2 patients excluded for lack of demographic data.

¶2 patients excluded due to extension of fusion to the thoracic spine.

Continues

Table 1. Continued

Author and Year	Number of Patients by Construct Type					
	Noninstrument	Wire or Cable Only	Wire and Rod	Screw and Rod	Hook and Rod	Screw and Wire
Lu et al., 2007 ⁴⁵	1					
Magrini et al., 2008 ⁴⁶	1					
Giussani et al., 2009 ⁴⁷		1				
Heuer et al., 2009 ⁴⁸				2		
Visocchi et al., 2009 ⁴⁹			5			
Hankinson et al., 2010 ⁵⁰				1		
Hedequist et al., 2010 ⁵¹			2			
Kuroki et al., 2012 ⁵²				2		
Dedlow et al., 2013 ⁵³				1		
Johnson et al., 2013 ⁵⁴				1		
Kosnik-Infinger et al., 2014 ⁵⁵				1		
Odent et al., 2014 ⁵⁶				1		
Siemionow et al., 2014 ⁵⁷				2		
Molinari et al., 2015 ⁵⁸				1		
Ito et al., 2017 ⁵⁹				2		
Siemionow et al., 2017 ^{4,¶}		1		6		3
Takeshima et al., 2017 ⁶⁰				1		

*1 patient excluded for follow-up <3 months.
†1 patient excluded due to lack of atlantoaxial instability.
‡1 patient excluded due to lack of neurologic status.
§2 patients excluded due to duplication in another included study.
||2 patients excluded for lack of demographic data.
¶2 patients excluded due to extension of fusion to the thoracic spine.

binary data using N-1 two proportion tests on pairs. The NIF, HRF, and SWF groups yielded an insufficient number of patients for comparative statistical analysis.

RESULTS

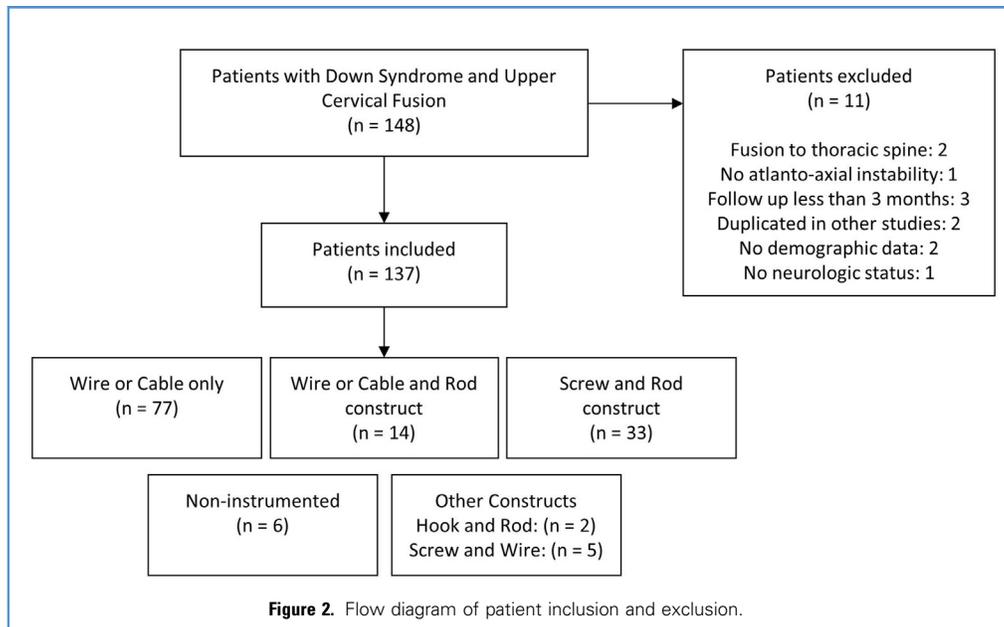
A total of 1191 publications were identified (Figure 1), of which 211 duplicates were removed. Of the remaining 980 articles, 900 were eliminated after title and abstract screening, yielding 80 articles that underwent full text review. A total of 29 of these were deemed unusable and removed: lack of demographic data (2 articles); no preoperative neurologic status (2); clinical details not assigned to individual patients (7); no recorded postoperative follow-up data (12); inadequate description of the type of fusion construct used (3); and only included duplicate patients (3). The remaining 51 case reports and case series, published from 1966–2017, were included for analysis (Table 1). All included studies were level IV evidence.⁶¹

These 51 articles yielded 148 patients with DS who underwent upper cervical fusion (Figure 2). Of these, 11 were excluded from analysis: 2 for fusion to the thoracic spine, 1 for atlantooccipital instability (AOI) without AAI, 3 for follow-up <3 months, 2 for

duplication in other included studies, 2 for lack of demographic data, and 1 for lack of documented preoperative neurologic status. The remaining 137 patients with DS and AAI treated with upper cervical fusion were included in the final analysis. The mean age was 13.2 years (standard deviation [SD]: 10.6), 54.7% of patients were female, and mean follow-up time was 37.6 months.

Wire-Only Fixation

A total of 77 patients underwent upper cervical fusion with WOF.^{4,10,12-15,18-30,33-35,38,39,47} The mean age was 12.1 years (SD: 9.9), 58.4% were female, mean follow-up was 36.5 months, and mean year of publication was 1992 (range: 1966–2017). Three patients had concurrent AOI. Arthrodesis was performed to the occiput in 64.5% of patients, the mean number of motion segments fused was 1.4, and 75.3% of patients were placed in a Halo orthosis. Of the 60 patients with grafting materials listed, 96.7% had autograft, 3.3% had allograft, and none had the addition of BMP. Preoperative neurologic dysfunction was present in 71.4% (Table 2). Loss of reduction or pseudoarthrosis occurred in 41.6%, early neurologic deterioration occurred in 24.7%, and late neurologic deterioration occurred in 2.6%. A total of 34 revision



operations were performed in 29 (37.7%) patients, with 11.7% having multiple revision surgeries. The bony union rate was 80.5% at last follow-up, at which time 7.8% of patients were neurologically worse, 7.8% had no change in preoperative deficit, 15.6% had partial improvement of their deficit, and 59.7% had normal neurologic function. The mortality rate was 9.1% (Table 3).

Wire-and-Rod Fixation

A total of 14 patients underwent upper cervical fusion with WRF.^{13,31,42,43,49,51} The mean age was 9.7 years (SD: 6.4), 64.3% were female, mean follow-up time was 36.1 months, and mean year of publication was 2004 (range: 1995–2010). One patient had concurrent AOI. Arthrodesis was extended to the occiput in all patients, the mean number of motion segments fused was 2.6, and 57.1% of patients were placed in a Halo orthosis. Of the 12 patients with grafting materials listed, all had autograft and none had allograft nor BMP. Preoperative neurologic dysfunction was present in 71.4% of patients (see Table 2). Loss of reduction or pseudoarthrosis occurred in 50%, early neurologic deterioration occurred in 7.1%, and late neurologic deterioration was not seen in any patients. A total of 4 revision surgeries were performed in 3 (21.4%) patients, with 7.1% having multiple revisions. The bony union rate was 100% at last follow-up, at which time no patients were neurologically worse, 7.1% had no change in preoperative deficit, 14.3% had partial improvement of their deficit, and 78.6% had normal neurologic function. No mortalities were reported (see Table 3).

Compared with patients with WOF, there was no significant difference in age ($P = 0.25$), gender ($P = 0.34$), or rate of preoperative neurologic dysfunction ($P = 0.5$). The number of motion segments fused ($P < 0.001$) and rate of fusion to the occiput ($P < 0.001$) were significantly higher. There was no difference in the types of grafts used or mean follow-up time. There was a trend toward lower rates of Halo use ($P = 0.08$) and early neurologic

decline ($P = 0.07$), but neither was significant. The mean year of publication was significantly more recent ($P < 0.001$). There was no significant difference in rates of complications, mortality, or revision surgery. Neurologic outcomes were similar between the 2 groups. Patients with wire-and-rod constructs had a significantly higher rate of bony union ($P = 0.036$).

Screw Fixation

A total of 33 patients underwent fusion using SF.^{4,13,36,37,41,44,48,50,52,54-60} The mean age was 15.7 years (SD: 11.1), 45.5% were female, the mean follow-up time was 33.2 months, and mean year of publication was 2009 (range: 1999–2017). One patient had concurrent AOI, and 2 had concurrent subaxial degeneration. Arthrodesis was performed to the occiput in 39.4% of patients, the mean number of motion segments fused was 1.7, and 39.3% of patients were placed in a Halo orthosis. Of the 28 patients with grafting materials reported, 89.3% had autograft, 10.7% had allograft, and 10.7% had BMP. Preoperative neurologic dysfunction was present in 60.6% of patients (see Table 2). Loss of reduction or pseudoarthrosis occurred in 18.2%, early neurologic deterioration occurred in 3.0%, and later neurologic dysfunction occurred in 6.1% of patients. A total of 7 revision surgeries were performed in 7 patients. No patients had multiple revisions. The bony union rate was 100% at last follow-up, at which time 3% of patients had worsened neurologically, 6.1% had a stable preoperative deficit, 12.1% had partial improvement of a deficit, and 75.8% had normal neurologic function. The mortality rate was 3% (see Table 3).

Compared with patients with WOF, there was no significant difference in age ($P = 0.12$), gender ($P = 0.11$), or rate of preoperative neurologic dysfunction ($P = 0.13$). The number of motion segments fused was greater ($P = 0.039$), but the rate of fusion to the occiput was not ($P = 0.33$). There was no difference in the types of grafts used or mean follow-up time, although

Table 2. Comparative Statistics for Preoperative and Operative Data by Construct Type

	Wire Fixation*		Wire-and-Rod Fixation		Screw Fixation	
	Result		Result	P Value	Result	P Value
Number	77		14	—	33	—
Mean age (years) [†]	12.1 (9.9)		9.7 (6.4)	0.25	15.7 (11.1)	0.12
Pediatric patients	65 (84.4%)		24 (72.7%)	0.15	13 (92.8%)	0.41
Gender						
Female	45 (58.4%)		9 (64.3%)	0.34	15 (45.5%)	0.11
Symptoms						
Neurologic	55 (71.4%)		10 (71.4%)	0.5	20 (60.6%)	0.13
Torticollis	9 (11.7%)		2 (14.3%)	0.39	2 (6.1%)	0.18
Pain	15 (19.5%)		0	0.036	8 (24.2%)	0.29
Acute	15 (19.5%)		1 (7.1%)	0.134	4 (12.1%)	0.18
Progressive	13 (16.9%)		3 (21.4%)	0.34	6 (18.2%)	0.43
Transient	4 (5.2%)		0	0.51	1 (3.0%)	0.31
Surgery						
Motion segments [†]	1.4 (0.6)		2.6 (0.6)	<0.001	1.7 (0.7)	0.039
Fusion to occiput	27 (35.1%)		14 (100%)	<0.001	13 (39.4%)	0.33
Graft reported	60		12		28	
Autograft [‡]	58 (96.7%)		12 (100%)	0.69	25 (89.3%)	0.08
Allograft [‡]	2 (3.3%)		0	0.69	3 (10.7%)	0.34
BMP [‡]	0		0		3 (10.7%)	0.34
Orthosis						
Halo	58 (75.3%)		8 (57.1%)	0.08	13 (39.3%)	<0.001
Collar	0		4 (28.6%)	<0.001	8 (24.2%)	<0.001
Other	16 (20.8%)		2 (14.3%)	0.29	1 (3.0%)	0.009
None	3 (3.9%)		0	0.60	11 (33.3%)	<0.001
Mean follow-up (months) [§]	36.5 (3–131)		36.1 (3–79)	0.96	33.2 (3–156)	0.69
Year of publication [§]	1992 (1966–2017)		2004 (1995–2010)	<0.001	2009 (1999–2017)	<0.001

*For the purposes of statistical analysis, wire-only fixation was taken as the reference.

[†]Indicates standard deviation is presented in parentheses.

[‡]Percentages calculated as number reported for each graft type divided by total patients with graft reported.

[§]Indicates range is presented in parentheses.

there was a trend toward decreased use of autograft in this group ($P = 0.08$). The rate of Halo usage was significantly lower with screw-and-rod constructs ($P < 0.001$). The mean year of publication was significantly more recent ($P < 0.001$). The rate of revision surgery ($P = 0.047$) and number of patients with multiple revisions ($P = 0.02$) were significantly lower with screw-and-rod constructs, and the rate of bony union was significantly higher ($P = 0.003$). Rates of loss of reduction and pseudoarthrosis ($P = 0.009$) and early neurologic deterioration ($P = 0.004$) were also significantly lower. The rates of other complications and mortalities, as well as neurologic outcome, were not significantly different.

Noninstrumented Fusion, Hook-and-Rod Fixation, and Screw-and-Wire Fixation

Six patients underwent upper cervical NIF for AAI.^{12,14,21,45,46} Two patients had fusion with HRF.^{32,38} Five patients had fusion with SWF.^{4,44} Their characteristics are described in **Tables 4** and **5**.

DISCUSSION

This review of the literature demonstrates the numerous small series that have been published on the surgical treatment of AAI in patients with DS. No prior meta-analyses of these data have been performed, but numerous fusion strategies including NIF,⁴⁶

Table 3. Comparative Statistics for Postoperative Outcomes by Construct Type

	Wire Fixation*		Wire-and-Rod Fixation		Screw Fixation	
	Result		Result	P Value	Result	P Value
Number	77		14	—	33	—
Revisions	34		4		7	
Patients with any	29 (37.7%)		3 (21.4%)	0.12	7 (21.2%)	0.047
Patients with >1	9 (11.7%)		1 (7.1%)	0.31	0	0.02
Bony union	62 (80.5%)		14 (100%)	0.036	33 (100%)	0.003
Complications						
LOR or pseudo	32 (41.6%)		7 (50.0%)	0.28	6 (18.2%)	0.009
Early neuro	19 (24.7%)		1 (7.1%)	0.07	1 (3.0%)	0.004
Late neuro	2 (2.6%)		0	0.71	2 (6.1%)	0.19
ICH	1 (1.3%)		0	0.85	0	0.51
Radiculopathy	0		0		1 (3.0%)	0.12
Hardware failure	5 (6.5%)		0	0.42	3 (9.1%)	0.32
Infection	4 (5.2%)		1 (7.1%)	0.57	2 (6.1%)	0.43
Cardiac	1 (1.3%)		0	0.85	0	0.51
Respiratory failure	7 (9.1%)		0	0.12	1 (3.0%)	0.13
Adjacent segment	6 (7.8%)		2 (14.3%)	0.22	2 (6.1%)	0.37
CSF leak	0		1 (7.1%)	0.15	0	
Decubitus ulcer	1 (2.3%)		0	0.85	0	0.51
Halo complication	3 (3.9%)		0	0.60	0	0.25
DVT	0		0		1 (3.0%)	0.12
UTI	1 (1.3%)		0	0.85	0	0.51
Pneumonia	2 (2.6%)		0	0.71	2 (6.1%)	0.19
Dysphagia	0		0		1 (3.0%)	0.12
Mortality	7 (9.1%)		0	0.12	1 (3.0%)	0.13
Outcome						
Worse	6 (7.8%)		0	0.36	1 (3.0%)	0.18
No change	6 (7.8%)		1 (7.1%)	0.47	2 (6.1%)	0.37
Partial	12 (15.6%)		2 (14.3%)	0.45	4 (12.1%)	0.09
Full	46 (59.7%)		11 (78.6%)	0.09	25 (75.8%)	0.055

LOR, loss of reduction; ICH, intracerebral hemorrhage; CSF, cerebrospinal fluid; DVT, deep venous thrombosis; UTI, urinary tract infection.
*For the purposes of statistical analysis, wire construct was taken as the reference.

WOF,^{4,47} WRF,^{49,51} SF,^{4,48,50,52-58,60} and SWF⁴ have been described and used within the past decade. This reflects the diversity of opinion regarding optimal treatment strategies for these patients. That many of these patients are treated as children or adolescents only amplifies this lack of consensus.

This work demonstrates greater rates of fusion with lower rates of revision surgery, halo utilization, early neurologic deterioration, and loss of reduction and pseudoarthrosis for screw and rod constructs compared with wiring alone. This finding is intuitive

given the greater rigidity provided by pedicle and transarticular screw fixation, compared with hook-and-wire constructs in craniocervical fixation, as demonstrated by Oda et al.⁶² It should be noted, however, that these patients were more likely to have a fixation construct that extended beyond C1 and C2. It has been hypothesized that extending the atlantoaxial fixation to the occiput leads to greater stability, resulting in better maintenance of reduction and fusion.^{57,63} Rates of fusion to the occiput were similar between these groups.

Table 4. Descriptive Statistics for Preoperative and Operative Data for Noninstrumented Fusion, Hook-and-Rod Fusion, and Screw-and-Wire Fixation

	Noninstrumented*	Hook-and-Rod Fixation	Screw-and-Wire Fixation
	Result	Result	Result
Number	6	2	5
Mean age (years) [†]	10.9 (9.4)	7.5 (6.4)	27 (18.9)
Gender			
Female	2 (33.3%)	2 (100%)	2 (40.0%)
Symptoms			
Neurologic	4 (66.7%)	1 (50.0%)	4 (80.0%)
Torticollis	0	0	0
Pain	1 (16.7%)	1 (50.0%)	0
Acute	1 (16.7%)	1 (50.0%)	0
Progressive	2 (33.3%)	0	2
Transient	1 (16.7%)	0	0
Surgery			
Motion segments [‡]	2.3 (1.0)	1.0 (0.0)	2.2 (1.6)
Fusion to occiput	5 (83.3%)	0	2 (40.0%)
Graft reported	4	2	5
Autograft [‡]	4 (100%)	2 (100%)	4 (80.0%)
Allograft [‡]	0	0	1 (20.0%)
BMP [‡]	1 (25.0%)	0	1 (20.0%)
Orthosis			
Halo	5 (83.3%)	1 (50.0%)	5 (100%)
Collar	0	0	0
Other	0	1 (50.0%)	0
None	1 (16.7%)	0	0
Mean follow-up (months) [§]	50.2 (5–142)	82 (8–156)	61.6 (25–88)
Year of publication [§]	1996 (1979–2008)	1998 (1995–2002)	2012 (2006–2017)

*For the purposes of statistical analysis, wire-only fixation was taken as the reference.

[†]Indicates standard deviation is presented in parentheses.

[‡]Percentages calculated as number reported for each graft type divided by total patients with graft reported.

[§]Indicates range is presented in parentheses.

Adding stabilizing rods to a wire/cable construct resulted in a greater rate of bony union but had no impact on other outcome measures. This result is confounded by an increased number of motion segments fused and increased rate of fusion to the occiput. In addition, these patients had a significantly lower rate of preoperative pain compared with those who received wiring alone. Although statistically significant, it is unclear if this is clinically meaningful but could be suggestive of a reporting bias.

An additional confounding factor in these 3 groups is the year of publication. Patients with wire-and-rod or screw-and-rod constructs were more likely to be presented in more recent publications than those with wire-only constructs. This likely

represents the overarching trend in fixation strategies for AAI in DS (and in complex spine surgery in general), with surgeons favoring the additional stability provided by rods and screws, as an alternative to the high complication rates reported with noninstrumented and wire-only constructs in earlier series. In addition, more recent results may be better than those of earlier series due to more rigorous patient selection, improved medical therapies, and the advent of new technologies including improved preoperative imaging, stereotactic navigation, electrophysiologic monitoring, BMP, and endoscopic endonasal odontoid resection,^{4,46,52,58,60} which may not have been uniformly reported in this series.

Table 5. Descriptive Statistics for Postoperative Outcomes for Noninstrumented Fusion, Hook-and-Rod Fusion, and Screw-and-Wire Fixation

	<u>Noninstrumented*</u>	<u>Hook-and-Rod Fixation</u>	<u>Screw-and-Wire Fixation</u>
	Result	Result	Result
Number	6	2	5
Revisions	7	0	0
Patients with any	4 (66.7%)	0	0
Patients with >1	3 (50.0%)	0	0
Bony union	5 (83.3%)	2 (100%)	5 (100%)
Complications			
LOR or pseudo	4 (66.7%)	0	0
Early neuro	3 (50.0%)	0	0
Late neuro	0	0	0
ICH	0	0	0
Radiculopathy	0	0	0
Hardware failure	1 (16.7%)	0	0
Infection	0	1 (50.0%)	0
Cardiac	0	0	0
Respiratory failure	1 (16.7%)	0	0
Adjacent segment	0	0	1 (20.0%)
CSF leak	0	0	0
Decubitus ulcer	0	1 (50.0%)	0
Halo complication	1 (16.7%)	0	0
DVT	0	0	0
UTI	0	0	0
Pneumonia	0	0	0
Dysphagia	0	0	0
Mortality	0	0	0
Outcome			
Worse	2 (33.3%)	0	0
No change	0	0	1 (20.0%)
Partial	3 (50.0%)	1 (50.0%)	3 (60.0%)
Full	1 (16.7%)	1 (50.0%)	1 (20.0%)

LOR, loss of reduction; ICH, intracerebral hemorrhage; DVT, deep venous thrombosis; UTI, urinary tract infection.
*For the purposes of statistical analysis, wire construct was taken as the reference.

This study is limited by the significant limitations inherent to a meta-analysis: the data include case reports and small case series, nonuniform surgical techniques and reporting, and variable follow-up. Meta-analysis was not feasible for all fixation strategies due to limited data for several construct types. Although it is preferable to perform meta-analyses on collections of studies with a high level of evidence, strong randomization, and large sample size, no such data exist for this patient

population. The present work represents the first study to systematically review outcomes for patients with DS undergoing upper cervical and craniocervical fusion for AIS and provides important insight into the unique challenges associated with treating this group. Further prospective study with larger patient cohorts through interinstitutional cooperation is warranted in order to further elucidate optimal treatment strategies for this patient population.

CONCLUSION

This work demonstrates the benefit of screw-rod and wire-rod constructs over wire-only constructs in the treatment of AAI in DS with respect to rates of fusion, pseudoarthrosis, loss of

reduction, and early neurologic decline. At this time, further prospective study of surgical technique in this patient population is necessary in order to reduce complications and improve neurologic outcomes.

REFERENCES

- Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down syndrome. *Ment Retard Dev Disabil Res Rev.* 2007;13:221-227.
- Zemel BS, Papan M, Stallings VA, et al. Growth charts for children with Down syndrome in the United States. *Pediatrics.* 2015;136:1204.
- Yamazaki M, Okawa A, Hashimoto M, Aiba A, Someya Y, Kodama M. Abnormal course of the vertebral artery at the craniocervical junction in patients with Down syndrome visualized by three-dimensional CT angiography. *Neuroradiology.* 2008;50:485-490.
- Siemionow K, Hansdorfer M, Janusz P, Mardjetko S. Complications in adult patients with down syndrome undergoing cervical spine surgery using current instrumentation techniques and rhBMP-2: a long-term follow-up. *J Neurol Surg A Cent Eur Neurosurg.* 2017;78:113-123.
- Miller JD, Capustan BM, Lampard R. Changes at the base of skull and cervical spine in Down syndrome. *Can Assoc Radiol J.* 1986;37:85-89.
- Rasmussen SA, Whitehead N, Collier SA, Frias JL. Setting a public health research agenda for Down syndrome: summary of a meeting sponsored by the centers for disease control and prevention and the national Down syndrome society. *Am J Med Genet A.* 2008;146A:2998-3010.
- Martich V, Ben-Ami T, Yousefzadeh DK, Roizen NJ. Hypoplastic posterior arch of C-1 in children with Down syndrome: a double jeopardy. *Radiology.* 1992;183:125-128.
- Bull MJ, Committee on Genetics. Health supervision for children with Down syndrome. *Pediatrics.* 2011;128:393-406.
- Cronk C, Crocker AC, Puschel SM, et al. Growth charts for children with Down syndrome: 1 month to 18 years of age. *Pediatrics.* 1988;81:102-110.
- Briggs RG, Carlson WO, Johnson DL. Atlantoaxial instability in Down's syndrome: a case report and review. *S D J Med.* 1992;45:279-282.
- El-Khoury M, Mourao MA, Tobo A, Battistella LR, Herrero CF, Riberto M. Prevalence of atlanto-occipital and atlantoaxial instability in adults with Down syndrome. *World Neurosurg.* 2014;82:215-218.
- Doyle JS, Lauerman WC, Wood KB, Krause DR. Complications and long-term outcome of upper cervical spine arthrodesis in patients with Down syndrome. *Spine (Phila Pa 1976).* 1996;21:1223-1231.
- Nader-Sepahi A, Casey AT, Hayward R, Crockard HA, Thompson D. Symptomatic atlantoaxial instability in Down syndrome. *J Neurosurg.* 2005;103:231-237.
- Segal LS, Drummond DS, Zanotti RM, Ecker ML, Mubarak SJ. Complications of posterior arthrodesis of the cervical spine in patients who have Down syndrome. *J Bone Joint Surg Am.* 1991;73:1547-1554.
- Shikata J, Yamamuro T, Mikawa Y, Iida H, Kobori M. Atlanto-axial subluxation in down's syndrome. *Int Orthop.* 1989;13:187-192.
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
- Dzenitis AJ. Spontaneous atlanto-axial dislocation in a mongoloid child with spinal cord compression. Case report. *J Neurosurg.* 1966;25:458-460.
- Curtis BH, Blank S, Fisher RL. Atlantoaxial dislocation in Down's syndrome: report of two patients requiring surgical correction; 4232523. *JAMA.* 1968;205:464-465.
- Finerman GA, Sakai D, Weingarten S. Atlanto-axial dislocation with spinal cord compression in a mongoloid child. A case report. *J Bone Joint Surg Am.* 1976;58:408-409.
- Holmes JC, Hall JE. Fusion for instability and potential instability of the cervical spine in children and adolescents. *Orthop Clin North Am.* 1978;9:923-943.
- Giblin PE, Micheli LJ. The management of atlanto-axial subluxation with neurologic involvement in Down's syndrome: a report of two cases and review of the literature. *Clin Orthop Relat Res.* 1979;140:66-71.
- Nordt JC, Stauffer ES. Sequelae of atlantoaxial stabilization in two patients with Down's syndrome. *Spine (Phila Pa 1976).* 1981;6:437-440.
- Shield LK, Dickens DRV, Jensen F. Atlantoaxial dislocation with spinal cord compression in Down syndrome. *J Paediatr Child Health.* 1981;17:114-116.
- Herring JA. Cervical instability in Down's syndrome and juvenile rheumatoid arthritis. *J Pediatr Orthop.* 1982;2:205-207.
- Sherk HH, Pasquariello PS, Watters WC. Multiple dislocations of the cervical spine in a patient with juvenile rheumatoid arthritis and Down's syndrome. *Clin Orthop Relat Res.* 1982;162:37-40.
- Koop SE, Winter RB, Lonstein JE. The surgical treatment of instability of the upper part of the cervical spine in children and adolescents. *J Bone Joint Surg Am.* 1984;66:403-411.
- Kobori M, Takahashi H, Mikawa Y. Atlanto-axial dislocation in Down's syndrome. Report of two cases requiring surgical correction. *Spine (Phila Pa 1976).* 1986;11:195-200.
- Chaudhry V, Sturgeon C, Gates AJ, Myers G. Symptomatic atlantoaxial dislocation in Down's syndrome. *Ann Neurol.* 1987;21:606-609.
- Smith MD, Phillips WA, Hensinger RN. Fusion of the upper cervical spine in children and adolescents. an analysis of 17 patients. *Spine (Phila Pa 1976).* 1991;16:695-701.
- Menezes AH, Ryken TC. Craniocervical abnormalities in Down's syndrome. *Pediatr Neurosurg.* 1992;18:24-33.
- Higo M, Sakou T, Taketomi E, Kojyo T. Occipitocervical fusion by luque loop rod instrumentation in Down syndrome. *J Pediatr Orthop.* 1995;15:539-542.
- Kohno M, Takahashi H, Yamakawa K, Ishijima B, Mitsui H. Instrumentational posterior fusion for atlanto-axial subluxation in a young child with Down's syndrome—case report. *Neurol Med Chir (Tokyo).* 1995;35:753-758.
- Hui JHP, Wong HK, Lee EH. High cervical spine instability in children with Down syndrome: a report of six cases and review of current management. *J Orthopaed Surg.* 1997;5:73-79.
- Lowry DW, Pollack IF, Clyde B, Albright AL, Adelson PD. Upper cervical spine fusion in the pediatric population; 9347973. *J Neurosurg.* 1997;87:671-676.
- Tseng SH, Cheng Y. Occiput-cervical fusion for symptomatic atlantoaxial subluxation in a 32-month-old child with Down syndrome: a case report. *Spinal Cord.* 1998;36:520-522.
- Brockmeyer DL, Apfelbaum RI. A new occipitocervical fusion construct in pediatric patients with occipitocervical instability: technical note. *J Neurosurg.* 1999;90:271-275.
- Pait TG, Al-Mefty O, Boop FA, Arnaoutovic KI, Rahman S, Ceola W. Inside-outside technique for posterior occipitocervical spine instrumentation and stabilization: preliminary results. *J Neurosurg.* 1999;90:1-7.
- Cohen MW, Drummond DS, Flynn JM, Pill SG, Dormans JP. A technique of occipitocervical arthrodesis in children using autologous rib grafts. *Spine.* 2001;26:825-829.
- Parisini P, Di Silvestre M, Gregg T, Bianchi G. C1-C2 posterior fusion in growing patients: long-term follow-up. *Spine.* 2003;28:566-571.
- Masuda K, Iwasaki M, Seichi A, Kitagawa T, Nakajima S, Kawaguchi H, Ohnishi I, Nakamura K. Cervical myelopathy in an adult due to atlantoaxial subluxation associated with Down syndrome: a case study. *J Orthop Sci.* 2003;8:227-231.
- Singh SK, Rickards L, Apfelbaum RI, Hurlbert RJ, Maiman D, Fehlings MG. Occipitocervical

- reconstruction with the Ohio medical instruments loop: results of a multicenter evaluation in 30 cases. *J Neurosurg.* 2003;98:239-246.
42. Visocchi M, Di Rocco F, Meglio M, Maciejczak Tamow A. Craniocervical junction instability: instrumentation and fusion with titanium rods and sublaminar wires. Effectiveness and failures in personal experience. *Acta Neurochir.* 2003;145:265-272.
 43. Yamazaki M, Koda M, Yoneda M, Aiba A, Moriya H. Anomalous vertebral artery at the craniovertebral junction in a patient with Down syndrome. Case report. *J Neurosurg Spine.* 2004;1:338-341.
 44. Reilly CW, Choit RL. Transarticular screws in the management of C1-C2 instability in children. *J Pediatr Orthop.* 2006;26:582-588.
 45. Lu DC, Sun PP. Bone morphogenetic protein for salvage fusion in an infant with down syndrome and craniovertebral instability: case report. *J Neurosurg.* 2007;106:480-483.
 46. Magrini S, Pasquini E, Mazzatenta D, Mascari C, Galassi E, Frank G. Endoscopic endonasal odontoidectomy in a patient affected by Down syndrome: technical case report. *Neurosurgery.* 2008;63:4.
 47. Giussani C, Roux FE, Guerra P, et al. Severely symptomatic craniovertebral junction abnormalities in children: long-term reliability of aggressive management. *Pediatr Neurosurg.* 2009;45:29-36.
 48. Heuer GG, Hardesty DA, Bhowmick DA, Bailey R, Magge SN, Storm PB. Treatment of pediatric atlantoaxial instability with traditional and modified Goel-harms fusion constructs. *Eur Spine J.* 2009;18:884-892.
 49. Visocchi M, Pietrini D, Tufo T, Fernandez E, Di Rocco C. Pre-operative irreducible C1-C2 dislocations: intra-operative reduction and posterior fixation. The "always posterior strategy.". *Acta Neurochir.* 2009;151:551-560.
 50. Hankinson TC, Anderson RC. Craniovertebral junction abnormalities in Down syndrome. *Neurosurgery.* 2010;66:32-38.
 51. Hedequist D, Bekelis K, Emans J, Proctor MR. Single stage reduction and stabilization of basilar invagination after failed prior fusion surgery in children with Down's syndrome. *Spine (Phila Pa 1976).* 2010;35:128.
 52. Kuroki H, Kubo S, Hamanaka H, Chosa E. Posterior occipito-axial fixation applied C2 laminar screws for pediatric atlantoaxial instability caused by Down syndrome: report of 2 cases. *Int J Spine Surg.* 2012;6:210-215.
 53. Dedlow ER, Siddiqi S, Fillipps DJ, Kelly MN, Nackashi JA, Tuli SY. Symptomatic atlantoaxial instability in an adolescent with trisomy 21 (Down's syndrome). *Clin Pediatr (Phila).* 2013;52:633-638.
 54. Johnson CS, Wilson DN, Mobbs RJ. Successful cranio-cervical fusion in a patient with Down syndrome. *J Clin Neurosci.* 2013;20:329-330.
 55. Kosnik-Infinger L, Glazier SS, Frankel BM. Occipital condyle to cervical spine fixation in the pediatric population: report of 4 cases. *J Neurosurg Pediatr.* 2014;13:45-53.
 56. Odent T, Bou Ghosn R, Dusabe J, Zerah M, Glorion C. Internal fixation with occipital hooks construct for occipito-cervical arthrodesis. Results in 14 young or small children. *Eur Spine J.* 2014;24:94-100.
 57. Siemionow K, Chou D. To the occiput or not? C1-C2 ligamentous laxity in children with Down syndrome. *Evid Based Spine Care J.* 2014;5:112-118.
 58. Molinari RW, Molinari C. The use of bone morphogenetic protein in pediatric cervical spine fusion surgery: case reports and review of the literature. *Global Spine J.* 2015;6:e46.
 59. Ito K, Imagama S, Ito Z, et al. Screw fixation for atlantoaxial dislocation related to Down syndrome in children younger than 5 years. *J Pediatr Orthop B.* 2017;26:86-90.
 60. Takeshima Y, Shigematsu H, Konishi K, Nakagawa I, Motoyama Y, Nakase H. Posterior atlantoaxial fusion using a C2 transverse foramen-penetrating screw: a technical note. *Surg Neurol Int.* 2017;8:262.
 61. North American Spine Society. *Levels of evidence for primary research question; 2015.* Available at: <https://www.spine.org/Portals/0/Documents/ResearchClinicalCare/LevelsOfEvidence.pdf?ver=2015-05-20-152558-113>. Accessed January 19, 2019.
 62. Oda I, Abumi K, Sell LC, Haggerty CJ, Cunningham BW, McAfee PC. Biomechanical evaluation of five different occipito-atlanto-axial fixation techniques. *Spine (Phila Pa 1976).* 1999;24:2377-2382.
 63. Abumi K, Takada T, Shono Y, Kaneda K, Fujiya M. Posterior occipitocervical reconstruction using cervical pedicle screws and plate-rod systems. *Spine (Phila Pa 1976).* 1999;24:1425-1434.

Conflict of interest statement: G. Alexander Jones has received a grant from Medtronic through Loyola University Medical Center for an unrelated research project, owns stock in InVivo Therapeutics, received an honorarium for the Chicago Review Course, and has received compensation for travel expenses from the Cleveland Spine Review. Ryan C. Hofler and Nathan Pecoraro have no financial disclosures to report. No funding was provided for this study.

Received 5 November 2018; accepted 28 January 2019

Citation: *World Neurosurg.* (2019) 126:e125-e135.
<https://doi.org/10.1016/j.wneu.2019.01.267>

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

1878-8750/\$ - see front matter © 2019 Elsevier Inc. All rights reserved.