

Stridor in multiple system atrophy

Consensus statement on diagnosis, prognosis, and treatment

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Abstract

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by a combination of autonomic failure, cerebellar ataxia, and parkinsonism. Laryngeal stridor is an additional feature for MSA diagnosis, showing a high diagnostic positive predictive value, and its early occurrence might contribute to shorten survival. A consensus definition of stridor in MSA is lacking, and disagreement persists about its diagnosis, prognosis, and treatment. An International Consensus Conference among experts with methodological support was convened in Bologna in 2017 to define stridor in MSA and to reach consensus statements for the diagnosis, prognosis, and treatment. Stridor was defined as a strained, high-pitched, harsh respiratory sound, mainly inspiratory, occurring only during sleep or during both sleep and wakefulness, and caused by laryngeal dysfunction leading to narrowing of the rima glottidis. According to the consensus, stridor may be recognized clinically by the physician if present at the time of examination, with the help of a witness, or by listening to an audio recording. Laryngoscopy is suggested to exclude mechanical lesions or functional vocal cord abnormalities related to different neurologic conditions. If the suspicion of stridor needs confirmation, drug-induced sleep endoscopy or video polysomnography may be useful. The impact of stridor on survival and quality of life remains uncertain. Continuous positive airway pressure and tracheostomy are both suggested as symptomatic treatment of stridor, but whether they improve survival is uncertain. Several research gaps emerged involving diagnosis, prognosis, and treatment. Unmet needs for research were identified.

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Glossary

CPAP = continuous positive airway pressure; **DISE** = drug-induced sleep endoscopy; **IRCCS-ISNB** = Istituto di Ricovero e Cura a Carattere Scientifico delle Scienze Neurologiche di Bologna; **MSA** = multiple system atrophy; **MSA-C** = MSA-cerebellar; **MSA-P** = MSA-parkinsonian; **VPSG** = video polysomnography.

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by a variable combination of autonomic failure, cerebellar ataxia, and parkinsonian features, typically poorly responsive to levodopa. The diagnostic criteria define 3 degrees of certainty for diagnosis, possible, probable, and definite, and 2 phenotypes, parkinsonian (MSA-P) and cerebellar (MSA-C), according to the predominant feature at the time of evaluation.^{1,2} Causes of death in MSA commonly include bronchopneumonia, urosepsis, or sudden death that often occurs during sleep.²

Several sleep-related breathing disorders, including stridor and central and obstructive sleep apneas, frequently occur in MSA.^{3,4} Stridor has been included in the diagnostic criteria as additional feature for the diagnosis of possible MSA, showing a high diagnostic positive predictive value.⁵⁻⁷ A recent study has suggested that early stridor onset is an independent risk factor for shorter survival⁸; however, its prognostic role remains controversial.⁹⁻¹¹ This may be a consequence of the distinct design, population characteristics, and MSA diagnostic certainty (clinical vs autopsy based) across studies. Furthermore, the lack of a universal definition for stridor and a gold standard for its diagnostic assessment may explain result heterogeneity.

Two main options have been suggested for treating stridor: tracheostomy or continuous positive airway pressure (CPAP).⁵ Tracheostomy is currently preferred in the advanced disease stage for severe stridor and in case of stridor during wakefulness with immobile vocal cords on laryngoscopy.⁵ CPAP as a non-invasive therapy can be used for mild and moderate intensity stridor occurring during sleep and related obstructive apneas. However, guidelines for stridor management are lacking, and only a few studies have assessed the role of stridor treatment on survival.^{8,12-14} The “Istituto di Ricovero e Cura a Carattere Scientifico delle Scienze Neurologiche di Bologna” (IRCCS-ISNB) promoted an international consensus conference among experts in the field with methodological support, convened in Bologna, Italy, on October 6 and 7, 2017. The aims of the conference were to (1) determine criteria for the diagnosis of stridor and consequently define stridor in MSA, (2) define the prognostic value of stridor on MSA survival, (3) suggest therapeutic options for stridor, and (4) provide statements for future research after systematically reviewing evidence and identifying unmet needs for clinical practice and research gray zones.

Methods

The method was inspired by the US National Institutes of Health Consensus Development Program¹⁵ and adapted

from the Methodological Handbook of the Italian National Guideline System.¹⁶ The consensus conference method is recommended for addressing important clinical questions in the face of limited good quality evidence. The main outcome, a consensus statement, represents the collective opinions of an expert panel, derived from systematic review and discussion of available evidence.¹⁷ The organizer of the Bologna Consensus Conference was the IRCCS-ISNB, Italy. Planning and execution of the project was performed in 4 phases: (1) assignment, (2) scoping, (3) assessment, and (4) the consensus conference itself. All activities, from conception to realization, were completed between February and October 2017. During the same period, a parallel project on dysphagia in patients with MSA was performed.

In (1) the assignment phase, the entities and their roles were defined, and participants were nominated and invited. Four entities were appointed: (1) the Scientific Committee (6 members) planned and organized the whole project, nominated the Consensus Development Panel and Workgroup members, and chose the questions to be answered by the Workgroup; (2) the Technical Committee (2 members) established methods and rules of the Consensus Conference, assisted with defining questions, and performed the systematic review with evidence mapping; (3) 1 Workgroup of experts (8 members) focused on stridor, synthesized and integrated information from the systematic review before the consensus conference, provided shared answers to the proposed questions, and presented their findings during the Consensus Conference, including research gaps and a proposal for future research; and (4) the Consensus Development Panel (8 members) chaired the Consensus Conference, established presentation procedures, and provided final statements.

In (2) the scoping phase, the scope and the protocol for the systematic review (registered on PROSPERO database, PROSPERO 2018 CRD42018079084)¹⁸ and the protocol for the conference were defined. The Scientific Committee identified the topics and together with the Technical Committee formulated the questions to be addressed. The questions were framed according to the Problem/Patient/Population, Intervention/Indicator, Comparison, Outcome model.¹⁹

In (3) the assessment phase, the Technical Committee performed a systematic review with evidence mapping to assess the state of knowledge on stridor in MSA. The systematic review

was performed following accepted criteria for the good conduct and reporting of systematic reviews¹⁸ and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.²⁰ The descriptive map of available research evidence was performed by adapting the methodology reported by the Global Evidence Mapping Initiative,²¹ which involved detailed coding of included studies and in-depth syntheses of the available research. Studies eligible for inclusion were published studies of any kind of design reporting original data on subjects with MSA having stridor during sleep, dealing with diagnosis, prognosis, and/or treatment. Studies published in abstract form, narrative review, or concept papers were excluded. Published studies were identified from the National Library of Medicine's MEDLINE database, Elsevier's EMBASE database, and the Cochrane Central Register of Controlled Trials by means of specific search strategies, using a combination of exploded MeSH terms and free text combining the concepts of stridor in sleep and MSA (see protocol on PROSPERO for details). Reference lists of identified articles were reviewed to find additional references. All abstracts or full articles without electronic abstracts were reviewed independently by 2 reviewers to identify potentially relevant studies. Each study was classified according to various descriptors, including topic domain, sample size, design, presence of diagnostic criteria of the stridor, and level of evidence according to the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology (2011).²² Briefly, each study was graded according to its risk of bias from Class I (highest quality) to Class IV (lowest quality). Risk of bias was judged by assessing specific quality elements (i.e., study design, patient spectrum, data collection, and masking) for each clinical topic (diagnostic accuracy, prognostic accuracy, and therapeutic). Disagreement between the 2 reviewers was resolved by discussion.

The Technical Committee then sent to the Workgroup experts a detailed summary of the systematic review with evidence mapping, the questions, and the abstracts of the most prominent studies, classified by topic and quality. The workgroup produced draft answers to be discussed during the Consensus Conference.

The Consensus Conference (4) was held over 2 days (October 6 and 7, 2017) in Bologna. On the first day, the Consensus Development Panel established the rules for the open discussion meetings, appraised the state of knowledge on stridor in MSA and the preliminary answers provided by experts, and proposed future strategies for the publication of the consensus statements. During a contemporaneous closed meeting, the experts independently discussed and reached final answers to the questions assigned to them. Finally, an open discussion was held in which experts presented their findings and all participants debated openly to reach consensus regarding each topic and the need for further research. On the second day, the Consensus Development Panel drafted a summary of the findings in a closed session. The chairperson then reported the findings in an open session that

included the consensus conference participants and other members of the scientific community and officials from the organizing institution. Finally, experts gave a presentation on needs for future research.

Results

Systematic review with evidence mapping

The literature search was performed in July 2017 and retrieved 212 citations after duplicate removal (figure). Each retrieved article was screened to assess potential relevance, and 53 were reviewed from the full text for inclusion. A total of 42 studies finally met the prespecified inclusion criteria, and 34 were used as basis for the statements. The majority of studies on diagnosis and treatment were of Class IV quality; those on prognosis of Class III (tables 1–4). Most studies on diagnosis and treatment included fewer than 10 patients and were case series or case reports as design. The cohort design was used in the majority of prognosis studies.

Diagnosis of stridor

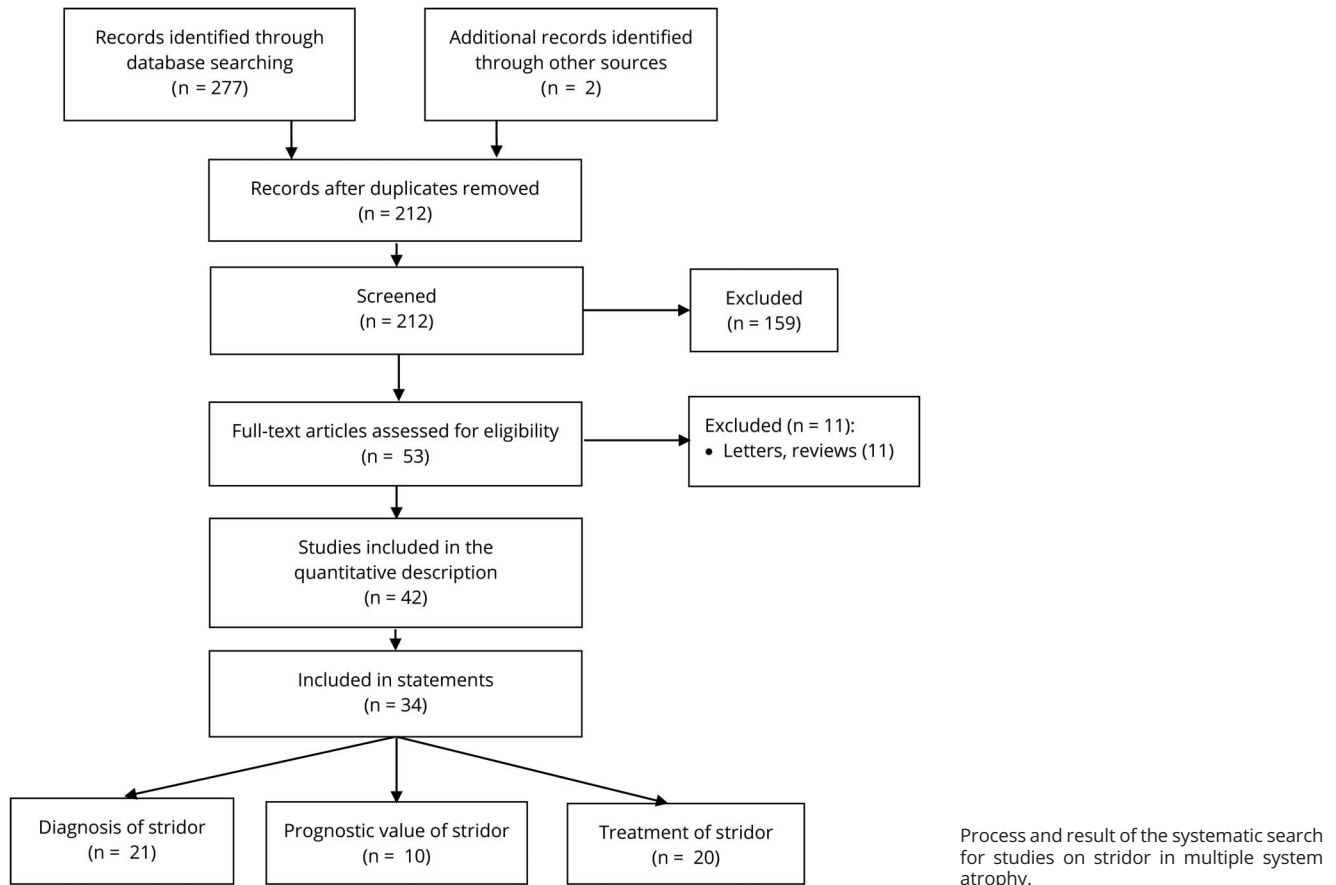
Stridor is a respiratory disturbance that in MSA typically occurs during sleep and might develop at any time point in the disease process. According to clinical and clinicopathologic studies, stridor prevalence in MSA ranges from 12% to 42%^{8–12,23–25} and is similar in MSA-C and MSA-P.^{8,9,11,12} In 2 studies, 4%–5.2% of patients presented stridor as an initial manifestation of MSA.^{8,26}

The clinical diagnosis of stridor remains challenging. The presence of a nighttime witness is typically necessary to suspect stridor because patients may be unaware of it. A high-pitched sound or heavy snoring are the symptoms frequently reported in patients who eventually turn out to have stridor, illustrating the problem of the differential diagnosis with snoring and obstructive sleep apnea syndrome, which are 2 other frequent sleep-related breathing disorders in MSA.^{3,4,10,24,27–29}

The term “peculiar snoring” was initially used to describe the distinctive noise occurring in MSA due to vibration of the vocal folds in inspiration, with a fundamental acoustic frequency of 260–330 Hz, different from that of ordinary soft palate snoring.³⁰ Subsequently, only a single study has analyzed the acoustic features of stridor in 22 patients with MSA by means of the Multi-Dimensional Voice Program.³¹ This study showed that stridor can be decomposed into rhythmic and semi-rhythmic waveforms. In both cases, it comprises formats and harmonics, whose presence suggests an origin in the vocal cords. In contrast, the sound analysis of snoring that was available for 18 of these patients revealed an irregular-shaped sound with no formats and harmonics.

Studies with video polysomnography (VPSG), which include audio recording and concurrent evaluation of vocal cord motion by fiberoptic laryngoscopy, showed that the high-pitched sound identified as stridor in patients with MSA was associated with impaired vocal cord abduction, paradoxical adduction, or both during inspiration and expiration, leading

Figure Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram



to narrowing of the rima glottidis. This indicates that inspiratory vibration of the narrowed vocal cord folds causes stridor.^{32–38}

In 1 VPSG study exploring breathing activity and EMG activity of the respiratory muscles, stridor was accompanied by overactivation of intercostalis and diaphragmatic muscles. In this study, the observation of tonic and subcontinuous muscle recruitment with phasing out of thoracic as opposed to abdominal respiratory traces with paradoxical inward movements of the abdominal wall during inspiration was suggestive of paradoxical breathing.³⁷

Further VPSG studies showed that other sleep-related respiratory disturbances such as snoring, central and obstructive sleep apneas, and breathing rate abnormalities (i.e., a pathologic breathing rate increase during non-REM and sleep) may occur in patients with MSA with and without stridor.^{12,24,33,37–39}

Laryngoscopy during wakefulness in patients with MSA with stridor, performed to exclude secondary causes or functional vocal cord abnormalities related to other neurologic conditions, can reveal bilateral or unilateral impairment of vocal

cord abduction of varying severity or normal vocal cord motility.^{27,29,32,33,35,36,39–44} Conversely, impairment of vocal cord motility during wakefulness was also observed in patients with MSA without stridor during sleep.²⁷

Studies with drug-induced sleep endoscopy (DISE) demonstrated impaired abduction or paradoxical adduction of the vocal cords in patients with MSA with stridor who had normal vocal cord motility on awake laryngoscopy.^{32,33,35–37,41–44}

Finally, a few studies have performed EMG of laryngeal muscles during wakefulness and drug-induced sleep. Patients with MSA with stridor could present normal EMG activity of adductor and abductor laryngeal muscles during quiet breathing and inspiration. Alternatively, they could show a neurogenic pattern of muscle unit action potential analysis of these muscles associated with tonic activity of adductor muscles during quiet breathing and paradoxical activity during inspiration. During drug-induced sleep, the main patterns were persistent tonic activity or paradoxical activation of laryngeal adductor muscles during inspiration.^{35–38,44–46}

Table 1 Descriptive features of eligible studies on stridor in MSA

	All studies	No. of patients = number of studies	Cohort studies	Case-control studies	Cross-sectional studies	Case series	Case report	Evidence class
Topic	N	N	N	N	N	N	N	
Diagnosis	24	<10 pts = 14 studies	—	2	5	10	7	All studies Class IV
		10–19 pts = 7 studies						
		20–50 pts = 3 studies						
Prognosis	11	<50 pts = 6 studies	10	—	—	1	—	2 Class II
		50–99 pts = 3 studies						8 Class III
		>100 pts = 2 studies						1 Class IV
Treatment	25	<10 pts = 12 studies	8	—	—	10	7	3 Class III
		10–19 pts = 6 studies						22 Class IV
		20–50 pts = 7 studies						

Abbreviation: MSA = multiple system atrophy; pts = patients.
Each study is graded according to its risk of bias from Class I to Class IV (with I being highest and IV lowest quality).

Statements on the diagnosis of stridor

Clinical features suggesting the presence of stridor

Statements are based on core literature consisting of Class IV level studies^{10,12,24,31} and expert opinion.

- Stridor is suspected when a high-pitched breathing sound is emitted by the patient during sleep or while awake, or when reported by caregivers.
- Stridor is probably underrecognized because patients and caregivers may be unaware of its presence, especially when it occurs at night.
- Recognition could be possible by the patient or caregiver after imitation of stridor by the physician (see supplementary sound track file, links.lww.com/WNL/A973).

Home audio recording to support the diagnosis of stridor

Statement is based on expert opinion because literature on the use of home audio recording to support the diagnosis of stridor (differential diagnosis of stridor from snoring) is lacking.

- Patients and caregivers should be encouraged to audio record episodes of suspected stridor.

VPSG to support the diagnosis of stridor

Statements are based on core literature consisting of Class IV level studies^{10,12,24,31,33,37–39} and expert opinion.

- VPSG including audio is not necessary if the physician has already diagnosed stridor.
- VPSG including audio may demonstrate stridor and its inspiratory nature.
- VPSG can characterize other sleep sounds.

Laryngoscopy for assessing stridor

Statements are based on core literature consisting of Class IV level studies^{27,29,32–37,39–44} and expert opinion.

- Laryngoscopy can exclude mechanical lesions (e.g., masses and scars) or functional vocal cord abnormalities related to different neurologic conditions (central or peripheral disorders).
- Laryngoscopy may reveal vocal cord motility impairment in patients with MSA with stridor.
- If awake laryngoscopy is normal, DISE might be considered if the suspicion of sleep-related stridor needs confirmation.

Other investigations for assessing stridor

Statements are based on core literature consisting of Class IV level studies^{35–38,44–46} and expert opinion.

- There is no evidence that other investigations are useful.
- EMG of the laryngeal muscles may show denervation or abnormal hyperactivity.

Conclusion on diagnostic criteria for stridor and definition of stridor in MSA

- Stridor in MSA is a strained, high-pitched, harsh respiratory sound, mainly inspiratory, caused by laryngeal dysfunction leading to narrowing of the rima glottidis. It may occur only during sleep or it may be present both during sleep and wakefulness.
- Stridor may be recognized clinically if present at the time of neurologic examination, with the help of a witness, or by listening to an audio recording.
- Laryngoscopy is suggested to exclude mechanical lesions (e.g., masses and scars) or functional vocal cord abnormalities related to different neurologic conditions (central or peripheral disorders).

Table 2 Studies that form the basis of the statements on diagnosis with their level of evidence

First author, y	Design	No. of patients	Diagnostic test	Diagnostic criteria of stridor	Level of evidence class
Alfonsi, 2016	Cross-sectional	17 (11 with stridor) + 40 normal controls	EMG; polysomnography	No	IV
Blumin, 2002	Case series	7	Fiberoptic laryngoscopy	No	IV
Chitose, 2012	Case report	1	Awake and sleep-induced laryngoscopy	No	IV
Hanson, 1983	Cross-sectional	12 (9 with stridor) + controls	Speech analysis	No	IV
Harcourt, 1996	Case series	18	Endoscopy; polysomnography	No	IV
Iranzo, 2004	Cross-sectional	40 (14 with stridor)	Polysomnography	No	IV
Isono, 2001	Case series	10	EMG under anesthesia and sleep	No	IV
Isozaki, 1996	Case-control	7	Awake and sleep-induced laryngoscopy	No	IV
Koo, 2016	Cross-sectional	22	Acoustic analysis	Yes	IV
Merlo, 2002	Case series	7	EMG pattern	No	IV
Nonaka, 2006	Case series	5	Sleep-induced laryngoscopy; EMG	No	IV
Sadaoka, 1996	Case-control	8	Polysomnography; esophageal pressure manometry/endoscopy	Yes	IV
Sadaoka, 1997	Case series	8	Acoustic analysis of snoring, polysomnography, fiberoptic examination under sedation	No	IV
Shiba, 2006	Case report	1	EMG	No	IV
Shimohata, 2006	Case report	1	Polysomnography	No	IV
Shimonata, 2007	Case series	21 (5 with stridor)	Polysomnography, laryngoscopy during wakefulness and under anesthesia	No	IV
Silber, 2000	Cross-sectional	42 (17 with stridor)	Polysomnography	Yes	IV
Stomeo, 2016	Case report	1	Sleep-induced endoscopy/sound analysis	No	IV
Vetruigno, 2004	Cross-sectional	19 (8 with stridor)	Polysomnography; intraesophageal pressure recording in 3 patients	Yes	IV
Vetruigno, 2007	Case series	3	Polysomnography including intraesophageal pressure recording; laryngoscopy; EMG	No	IV
Williams, 1979	Case series	12	Fiberoptic laryngoscopy	No	IV

Each study was classified according to various descriptors, including topic domain, sample size, design, presence of diagnostic criteria of the syndrome, and level of evidence according to the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology (2011). Each study was graded according to its risk of bias from Class I to Class IV (with I highest quality and IV lowest quality). Risk of bias was judged by assessing specific quality elements (i.e., study design, patient spectrum, data collection, and masking) for each clinical topic (diagnostic accuracy, prognostic accuracy, and treatment).

- If awake laryngoscopy is normal and the suspicion of sleep-related stridor needs confirmation, the following additional evaluations might be considered: (1) DISE

and (2) VPSG to document the inspiratory nature of the sound, the presence of expiratory intercostalis activation, or the presence of associated sleep breathing disorders.

Table 3 Studies that form the basis of the statements on prognosis with their level of evidence

First author, y	Design	No. of patients	Level of evidence
Coon, 2015	Cohort	685 (176 with stridor)	II
Giannini, 2016	Cohort	136 (42 with stridor)	III
Glasmacher, 2017	Systematic review	6 studies	Not available
Koo, 2016	Cohort	22	III
Krim, 2007	Cohort	86 (17 with stridor)	II
Lalich, 2014	Cohort	38 (25 with stridor)	III
Silber, 2000	Cohort	42 (30 with follow-up data, 11 with stridor)	III
Starhof, 2016	Cohort	99 (44 with stridor)	II
Tada, 2007	Cohort	49 (18 with stridor)	III
Yamaguchi, 2003	Cohort	83 (33 with stridor)	III

Each study was classified according to various descriptors, including topic domain, sample size, design, presence of diagnostic criteria of the syndrome, and level of evidence according to the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology (2011). Each study was graded according to its risk of bias from Class I to Class IV (with I highest quality and IV lowest quality). Risk of bias was judged by assessing specific quality elements (i.e., study design, patient spectrum, data collection, and masking) for each clinical topic (diagnostic accuracy, prognostic accuracy, and treatment).

Prognostic value of stridor

Retrospective cohort studies have reported conflicting results on the prognostic value of stridor.⁴⁷ Seven studies did not find an association between the presence of stridor during the disease course and shortened survival.^{8,9,11,14,48–50} In most of these studies, stridor was clinically suspected without instrumental confirmation. In contrast, 1 study showed shorter survival in patients with MSA with stridor after VPSG recording, but not from disease onset.¹⁰ Finally, the largest study with VPSG found that early onset of stridor (within 3 years from motor or autonomic symptom onset) was an independent predictor of shorter survival.⁸ Based on an analysis with the Multi-Dimensional Voice Program, 1 study reported that acoustic features of stridor may affect survival in MSA.³¹

Statements on the prognostic value of stridor

Effect of stridor on survival

Statements regarding the effect of stridor on survival in MSA are based on core literature consisting of Class II/III level studies,^{8–11,14,31,48–50} a systematic review,⁴⁷ and expert opinion.

- Whether stridor affects survival is uncertain.
- Stridor within 3 years of motor or autonomic symptom onset may shorten survival. However, identification of stridor onset may be difficult.
- Whether specific features of stridor affect survival remains to be determined.
- Stridor during wakefulness is widely considered to reflect a more advanced stage of the disease than stridor occurring during sleep.

Effect of stridor on well-being or health-related quality of life

Literature on the effect of stridor on well-being or health-related quality of life is lacking. Statements are based on expert opinion.

- Stridor can be distressing for patients and caregivers.
- The impact on health-related quality of life remains to be determined.

Treatment of stridor

Four retrospective studies reported that the treatment of stridor improves survival.^{8,12–14} Stridor treatment mainly comprised CPAP or tracheostomy.^{10,27,29,32,33,35,39,51,52} In 3 studies (<15 patients), CPAP initially eliminated stridor in almost all patients,^{12,13,51} but the long-term symptomatic effect remains unknown.

Three studies reported survival in patients with MSA treated with CPAP. In 1 small study, CPAP had no effect on survival.¹⁰ In another prospective cohort study, patients with MSA with stridor receiving CPAP (n = 13) had similar median survival compared with a group of patients with MSA without stridor (n = 26).¹² Sudden death was reported in 2 of 13 patients following CPAP initiation.¹³

Classic tracheostomy is usually the surgical procedure of choice for stridor. This involves the positioning of a fenestrated cannula, maintained closed during the day to allow phonation.⁵³ Alternative techniques such as skin-lined tracheostomy have recently been proposed for the treatment of severe stridor in MSA.⁵⁴ Skin-lined tracheostomy offers several advantages, such as a greater opening of the stoma, higher stability over time, less risk of granulation tissue, and reversibility. In addition, it does not require a cannula during the night, and the stoma is easy to plug during the day.

Three studies focused on the role of tracheostomy on survival. In the largest retrospective study (n = 42 with stridor), patients treated with tracheostomy had longer overall disease

Table 4 Studies that form the basis of the statements on therapy with their level of evidence

First author, y	Design	No. of patients	Treatment	Level of evidence
Blumin, 2002	Case series	7	CPAP: bilevel positive airway pressure; tracheostomy	IV
Chitose, 2012	Case report	1	CPAP; laser arytenoidectomy	IV
Ghorayeb, 2005	Case series	22 (15 with stridor)	CPAP	IV
Giannini, 2016	Cohort	136 (42 with stridor; 31 treated)	CPAP (19 pts); tracheostomy (12 pts)	III
Harcourt, 1996	Case series	18	CPAP (2 pts); tracheostomy (2 pts); arytenoidectomy (3 pts)	IV
Iranzo, 2000	Cohort	20 (5 with stridor)	CPAP	IV
Iranzo, 2004	Cohort	14 (with stridor)	CPAP (13 pts)	IV
Isono, 2001	Case series	10	CPAP on laryngeal resistance and muscle activity (6 pts)	IV
Isozaki, 1996	Case series	7	Tracheostomy	IV
Jin, 2007	Case series	18	Tracheostomy (7 pts)	IV
Kneisley, 1990	Case report	1	Arytenopexy; vocal cord pinning	IV
Lalich, 2014	Cohort	1	CPAP	IV
Mahmud, 2015	Case report	1	Laser arytenoidectomy and posterior cordotomy	IV
Merlo, 2002	Case series	7	Botulinum toxin (4 pts)	IV
Sadaoka, 1996	Case series	8	Tracheostomy	IV
Silber, 2000	Cohort	42 (30 with follow-up data)	CPAP (5 pts); tracheostomy (4 pts)	IV
Stomeo, 2016	Case report	1	Subtotal arytenoidectomy	IV
Tada, 2007	Cohort	18 (with stridor)	Tracheotomy (12 pts)	III
Williams, 1979	Case series	12	Tracheostomy (4 pts)	IV
Yamaguchi, 2003	Cohort	33 (with stridor; 15 treated)	CPAP; tracheostomy; laryngectomy	III

Abbreviation: CPAP = continuous positive airway pressure; pts = patients.

Each study was classified according to various descriptors, including topic domain, sample size, design, presence of diagnostic criteria of the syndrome, and level of evidence according to the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology (2011). Each study was graded according to its risk of bias from Class I to Class IV (with I highest quality and IV lowest quality). Risk of bias was judged by assessing specific quality elements (i.e., study design, patient spectrum, data collection, and masking) for each clinical topic (diagnostic accuracy, prognostic accuracy, and treatment).

duration, longer disease duration after stridor onset, and longer disease duration after treatment compared with those treated with CPAP.⁸ Another study showed that tracheostomy may reduce the risk of death and of sudden death in patients with MSA with stridor.¹¹ One study reported that 2 of the 4 patients with tracheostomy died 1 year after the sleep evaluation, whereas the other 2 were alive 1.9 and 7 years later.¹⁰

Single case reports have described the use of posterior cordotomy and arytenoidectomy,^{28,43,44,55} and botulinum toxin relieved dystonic stridor in 3 of 4 patients 1 month after inoculation.⁴⁵

Statements on the treatment of stridor

Treatment for symptomatic control of stridor

Statements are based on core literature consisting of Class III/IV level studies^{8,10–14,27,29,32,33,35,39,49,51,52} and expert opinion.

- Ventilation during sleep (CPAP) can be useful in the symptomatic control of stridor.

- Consider ventilation during sleep (CPAP) as a first-line symptomatic therapy.
- Tracheostomy bypasses upper airway obstruction at laryngeal level and relieves distressing stridor. Tracheostomy is effective in the symptomatic control of stridor.
- Persistent and severe stridor may require tracheostomy.

CPAP for improving survival of patients with stridor

Statement is based on core literature consisting of Class III/IV level studies.^{8,10,12,13}

- Whether CPAP improves survival in patients with MSA with stridor is uncertain.

Tracheostomy for improving survival of patients with stridor

Statement is based on core literature consisting of Class III/IV level studies.^{8,10,11}

- Tracheostomy might improve survival in patients with stridor.

Other treatment options for stridor

Statement is based on core literature consisting of Class IV level studies including case reports.^{28,43–45,55}

- There is insufficient evidence for minimally invasive procedures and botulinum toxin injections for the symptomatic treatment of stridor.

Research needs

The present Consensus Conference represents the first effort to systematically revise the literature and to provide statements on stridor, a specific feature of MSA, that could affect the disease course. However, despite the importance of this topic, the majority of studies available in the literature were of Class III–IV quality, leading also to statements based on expert opinions. Furthermore, several research gaps emerged during the consensus meeting concerning diagnosis, prognosis, and treatment for stridor.

One main challenge is the diagnosis of stridor. Whether the imitation of stridor by the physician during follow-up visits is sufficient to correctly and earlier identify stridor or whether other tools, such as specific questionnaires or a home audio recording, may improve diagnostic accuracy is unknown. This point could be of crucial importance if the negative prognostic role of early stridor onset is confirmed. It has also to be established when the use of VPSG is necessary for the diagnosis of stridor. For these reasons, a questionnaire for detecting stridor should be developed and its diagnostic accuracy be compared with VPSG in a multicenter prospective study. Similarly, the diagnostic accuracy of sound imitation by the physician or home audio recording should be evaluated. A smartphone application could be developed to automatically recognize the stridor sound. Finally, the place of DISE for early stridor detection requires further investigation, and the method to measure the progression of stridor over time should be standardized.

The relationship between stridor and other breathing disorders (i.e., central apneas and breathing rate abnormalities) and their respective contributions to disease prognosis and survival should be determined through a multicenter prospective study. VPSG should be used to determine stridor and breathing disorders in this study. Moreover, further studies could contribute to elucidate the role on survival of specific characteristic obtained from awake laryngoscopy, DISE, laryngeal EMG (denervation/muscle hyperactivity), and acoustic recordings. In addition, the contribution of stridor to patients and caregiver quality of life is unknown.

To guide the physician for the treatment of stridor, randomized controlled trials comparing the efficacy of CPAP and tracheostomy for different degrees of stridor are warranted. Studies using laryngoscopy and/or laryngeal EMG should be conducted to identify specific characteristics that may predict treatment tolerance and response. Moreover, the usefulness of CPAP for severe stridor, as well as technical aspects including titration, patient compliance, and the timing of follow-up need to be

determined. Finally, the usefulness of bilevel PAP should be compared with CPAP. Similarly to CPAP, interventional studies should also compare skin-lined vs conventional tracheostomy.

Literature revision and the emergence of several research gaps on diagnosis, prognosis, and treatment for stridor rise the need of prospective multicenter studies on large samples, and with a randomized controlled design concerning its treatment, to provide high level of evidence in the role of stridor in MSA course.

Author contributions

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References

1. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 2008;71:670–676.
2. Fanciulli A, Wenning GK. Multiple-system atrophy. *N Engl J Med* 2015;372:249–263.
3. Abbott SM, Videnovic A. Sleep disorders in atypical parkinsonism. *Mov Disord Clin Pract* 2014;1:89–96.
4. Iranzo A. Sleep and breathing in multiple system atrophy. *Curr Treat Options Neurol* 2007;9:347–353.
5. Ozawa T, Sekiya K, Aizawa N, Terajima K, Nishizawa M. Laryngeal stridor in multiple system atrophy: clinicopathological features and causal hypotheses. *J Neurol Sci* 2016;361:243–249.
6. Osaki Y, Ben-Shlomo Y, Lees AJ, Wenning GK, Quinn NP. A validation exercise on the new consensus criteria for multiple system atrophy. *Mov Disord* 2009;24:2272–2276.
7. Köllensperger M, Geser F, Seppi K, et al. Red flags for multiple system atrophy. *Mov Disord* 2008;23:1093–1099.
8. Giannini G, Calandra-Buonaura G, Mastrolilli F, et al. Early stridor onset and stridor treatment predict survival in 136 patients with MSA. *Neurology* 2016;87:1375–1383.
9. Coon EA, Sletten DM, Suarez MD, et al. Clinical features and autonomic testing predict survival in multiple system atrophy. *Brain* 2015;138:3623–3631.
10. Silber MH, Levine S. Stridor and death in multiple system atrophy. *Mov Disord* 2000;15:699–704.
11. Tada M, Onodera O, Tada M, et al. Early development of autonomic dysfunction may predict poor prognosis in patients with multiple system atrophy. *Arch Neurol* 2007;64:256–260.
12. Iranzo A, Santamaria J, Tolosa E, et al. Long-term effect of CPAP in the treatment of nocturnal stridor in multiple system atrophy. *Neurology* 2004;63:930–932.
13. Ghorayeb I, Yekhlief F, Bioulac B, Tison F. Continuous positive airway pressure for sleep-related breathing disorders in multiple system atrophy: long-term acceptance. *Sleep Med* 2005;6:359–362.
14. Yamaguchi M, Arai K, Asahina M, Hattori T. Laryngeal stridor in multiple system atrophy. *Eur Neurol* 2003;49:154–159.
15. Nair R, Aggarwal R, Khanna D. Methods of formal consensus in classification/diagnostic criteria and guideline development. *Semin Arthritis Rheum* 2011;41:95–105.
16. Candiani G, Colombo C, Daghini R, et al. Manuale metodologico: come organizzare una conferenza di consenso. Istituto Superiore di Sanità, Sistema Nazionale Linee Guida SNLG, Roma, Novembre 2009 [online]. Available at: medicinanarrativa.eu/wp-content/uploads/consensus_conference-1.pdf. Accessed September 29, 2018.
17. American College of Chest Physicians. Consensus Statement Methodology [online]. Available at: chestnet.org/Guidelines-and-Resources/About-CHEST-Guidelines/Guideline-Development. Accessed February 28, 2019.
18. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking systematic reviews in health care. 2009. Available at: york.ac.uk/crd/guidance/. Accessed February 28, 2019.
19. CEBM- Centre for Evidence-Based Medicine, PICO Structure. Available at: cebm.net/2014/06/asking-focused-questions/. Accessed February 28, 2019.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
21. Bragge P, Clavisi O, Turner T, Tavender E, Collie A, Gruen RL. The Global Evidence Mapping Initiative: scoping research in broad topic areas. *BMC Med Res Methodol* 2011;11:92.
22. AAN (American Academy of Neurology). Clinical Practice Guideline Process Manual, 2011. St. Paul: The American Academy of Neurology; 2011. Available at tools.aan.com/globals/axon/assets/9023.pdf. Accessed September 29, 2018.
23. Wenning GK, Ben Shlomo Y, Magalhães M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. *Brain* 1994;117(pt 4):835–845.
24. Vetrugno R, Provini F, Cortelli P, et al. Sleep disorders in multiple system atrophy: a correlative video-polysomnographic study. *Sleep Med* 2004;5:21–30.
25. Figueroa JJ, Singer W, Parsaik A, et al. Multiple system atrophy: prognostic indicators of survival. *Mov Disord* 2014;29:1151–1157.
26. Uzawa A, Sakakibara R, Tamura N, et al. Laryngeal abductor paralysis can be a solitary manifestation of multiple system atrophy. *J Neurol Neurosurg Psychiatry* 2005;76:1739–1741.
27. Williams A, Hanson D, Calne DB. Vocal cord paralysis in the Shy-Drager syndrome. *J Neurol Neurosurg Psychiatry* 1979;42:151–153.
28. Kneisley LW, Rederich GJ. Nocturnal stridor in olivopontocerebellar atrophy. *Sleep* 1990;13:362–368.
29. Blumin JH, Berke GS. Bilateral vocal fold paresis and multiple system atrophy. *Arch Otolaryngol Head Neck Surg* 2002;128:1404–1407.
30. Kakitsuba N, Sadaoka T, Kanai R, Fujiwara Y, Takahashi H. Peculiar snoring in patients with multiple system atrophy: its sound source, acoustic characteristics, and diagnostic significance. *Ann Otol Rhinol Laryngol* 1997;106:380–384.
31. Koo DL, Lee JY, Joo EY, Hong SB, Nam H. Acoustic characteristics of stridor in multiple system atrophy. *PLoS One* 2016;11:e0153935.
32. Isozaki E, Naito A, Horiguchi S, Kawamura R, Hayashida T, Tanabe H. Early diagnosis and stage classification of vocal cord abductor paralysis in patients with multiple system atrophy. *J Neurol Neurosurg Psychiatry* 1996;60:399–402.
33. Sadaoka T, Kakitsuba N, Fujiwara Y, Kanai R, Takahashi H. Sleep-related breathing disorders in patients with multiple system atrophy and vocal fold palsy. *Sleep* 1996;19:479–484.
34. Sadaoka T, Kakitsuba N, Fujiwara Y, Kanai R, Takahashi H. Limitation of vocal fold abduction only during sleep in a patient with Shy-Drager syndrome. *Am J Otolaryngol* 1997;18:145–147.
35. Isono S, Shiba K, Yamaguchi M, et al. Pathogenesis of laryngeal narrowing in patients with multiple system atrophy. *J Physiol (Lond)* 2001;536:237–249.
36. Nonaka M, Imai T, Shintani T, Kawamata M, Chiba S, Matsumoto H. Non-invasive positive pressure ventilation for laryngeal contraction disorder during sleep in multiple system atrophy. *J Neurol Sci* 2006;247:53–58.
37. Vetrugno R, Liguori R, Cortelli P, et al. Sleep-related stridor due to dystonic vocal cord motion and neurogenic tachypnea/tachycardia in multiple system atrophy. *Mov Disord* 2007;22:673–678.
38. Alfonsi E, Terzaghi M, Cosentino G, et al. Specific patterns of laryngeal electromyography during wakefulness are associated to sleep disordered breathing and nocturnal stridor in multiple system atrophy. *Parkinsonism Relat Disord* 2016;31:104–109.
39. Harcourt J, Spraggs P, Mathias C, Brookes G. Sleep-related breathing disorders in the Shy-Drager syndrome. Observations on investigation and management. *Eur J Neurol* 1996;3:186–190.
40. Hanson DG, Ludlow CL, Bassich CJ. Vocal fold paresis in Shy-Drager syndrome. *Ann Otol Rhinol Laryngol* 1983;92:85–90.
41. Shimohata T, Nakayama H, Shinoda H, et al. Multiple system atrophy with progressive nocturnal hypoxemia: case report with polysomnography and continuous positive airway pressure treatment. *Eur Neurol* 2006;56:258–260.
42. Shimohata T, Shinoda H, Nakayama H, et al. Daytime hypoxemia, sleep-disordered breathing, and laryngopharyngeal findings in multiple system atrophy. *Arch Neurol* 2007;64:856–861.
43. Chitose S, Kikuchi A, Ikezono K, Umeno H, Nakashima T. Effect of laser arytenoidectomy on respiratory stridor caused by multiple system atrophy. *J Clin Sleep Med* 2012;8:713–715.
44. Stomeo F, Rispoli V, Sensi M, Pastore A, Malagutti N, Pelucchi S. Subtotal arytenoidectomy for the treatment of laryngeal stridor in multiple system atrophy: pharyngeal and swallowing results. *Braz J Otorhinolaryngol* 2016;82:116–120.
45. Merlo IM, Occhini A, Pacchetti C, Alfonsi E. Not paralysis, but dystonia causes stridor in multiple system atrophy. *Neurology* 2002;58:649–652.
46. Shiba K, Isono S. Tracheostomy abolishes paradoxical activation of the vocal cord adductor in multiple system atrophy. *Auris Nasus Larynx* 2006;33:295–298.
47. Glasmacher SA, Leigh PN, Saha RA. Predictors of survival in progressive supranuclear palsy and multiple system atrophy: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2017;88:402–411.
48. Krim E, Yekhlief F, Chrysostome V, Ghorayeb I, Tison F. Multiple system atrophy: prognostic factors in the “MSA- Aquitaine” cohort. *Rev Neurol* 2007;163:54–65.
49. Lalich IJ, Ekbom DC, Starkman SJ, Orbelo DM, Morgenthaler TI. Vocal fold motion impairment in multiple system atrophy. *Laryngoscope* 2014;124:730–735.
50. Starhof C, Korbo L, Funch Lassen C, Winge K, Friis S. Clinical features in a Danish population-based cohort of probable Multiple System Atrophy patients. *Neuroepidemiology* 2016;46:261–267.
51. Iranzo A, Santamaria J, Tolosa E. Continuous positive air pressure eliminates nocturnal stridor in multiple system atrophy. *Barcelona Multiple System Atrophy Study Group. Lancet* 2000;356:1329–1330.
52. Jin K, Onodera H, Chida K, Abe N, Itoyama Y. Spade-shaped vocal cord in a multiple system atrophy patient with nocturnal stridor. *Intern Med* 2007;46:921.
53. Kuhlo W, Doll E, Franck MC. Successful management of Pickwickian syndrome using long-term tracheostomy [in German]. *Dtsch Med Wochenschr* 1969;94:1286–1290.
54. Campanini A, De Vito A, Frassinetti S, Vicini C. Role of skin-lined tracheostomy in obstructive sleep apnoea syndrome: personal experience. *Acta Otorhinolaryngol Ital* 2004;24:68–74.
55. Mahmud A, Strens LH, Tedla M. Laser arytenoidectomy and posterior cordotomy in a patient with bilateral vocal cord paralysis due to multiple system atrophy. *BMJ Case Rep* 2015;2015:1–3.

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