Laryngeal Injury and Upper Airway Symptoms After Oral Endotracheal Intubation With Mechanical Ventilation During Critical Care: A Systematic Review

Martin B. Brodsky, PhD, ScM[1,2]; Matthew J. Levy, DO, MSc[3]; Erin Jedlanek, MS[1]; Vinciya Pandian, PhD, MBA, MSN[2,4]; Brendan Blackford, MHS[5]; Carrie Price, MLS[6]; Gai Cole, DrPH, MBA, MHA[3]; Alexander T. Hillel, MD[7]; Simon R. Best, MD[7]; Lee M. Akst, MD[7]

Objectives: To systematically review the symptoms and types of laryngeal injuries resulting from endotracheal intubation in mechanically ventilated patients in the ICU.

Data Sources: PubMed, Embase, CINAHL, and Cochrane Library from database inception to September 2017.

Study Selection: Studies of adult patients who were endotracheally intubated with mechanical ventilation in the ICU and completed postextubation laryngeal examinations with either direct or indirect visualization.

Data Extraction: Independent, double-data extraction and risk of bias assessment followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Risk of bias assessment followed the Cochrane Collaboration's criteria.

Data Synthesis: Nine studies (seven cohorts, two cross-sectional) representing 775 patients met eligibility criteria. The mean (SD; 95% CI) duration of intubation was 8.2 days (6.0 d; 7.7–8.7 d). A high prevalence (83%) of laryngeal injury was found. Many of these were mild injuries, although moderate to severe injuries occurred in 13–31% of patients across studies. The most frequently occurring clinical symptoms reported post extubation were dysphonia (76%), pain (76%), hoarseness (63%), and dysphagia (49%) across studies.

Conclusions: Laryngeal injury from intubation is common in the ICU setting. Guidelines for laryngeal assessment and postextubation surveillance do not exist. A systematic approach to more robust investigations could increase knowledge of the association between particular injuries and corresponding functional impairments, improving understanding of both time course and prognosis for resolution of injury. Our findings identify targets for future research and highlight the long-known, but understudied, clinical outcomes from endotracheal intubation with mechanical ventilation in ICU. (*Crit Care Med* 2018; XX:00–00)

Key Words: deglutition; endotracheal intubation; intensive care; larynx; voice

Globally, there are 13–20 million critically ill patients intubated in ICUs annually (1). Similar to many medical treatments, the iatrogenic effects of intubation have potential for acute and chronic symptoms, and both short- and long-term harms requiring further medical care that extends beyond ICU discharge.

Patient complaints frequently include hoarseness, loss of voice, throat clearing, sore throat, and vocal fatigue post

[1]Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD.

[2]Outcomes After Critical Illness and Surgery (OACIS) Research Group, Johns Hopkins University, Baltimore, MD.

[3]Department of Emergency Medicine, Johns Hopkins University, Baltimore, MD.

[4]Department of Acute and Chronic Care-School of Nursing, Johns Hopkins University, Baltimore, MD.

[5]Department of Medicine, Johns Hopkins University, Baltimore, MD.

[6]Welch Medical Library, Johns Hopkins University, Baltimore, MD.

[7]Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University, Baltimore, MD.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Supported, in part, by the National Institutes of Health/National Institute on Deafness and Other Communication Disorders (5K23DC013569, Dr. Brodsky).

Dr. Brodsky's institution received funding from National Institutes of Health (NIH)/National Institute on Deafness and Other Communication Disorders, and he received funding from MedBridge. Drs. Brodsky, Pandian, and Hillel received support for article research from the NIH. Dr. Pandian's institution received funding from Smiths Medical and other consulting work. Dr. Hillel received funding from Olympus USA. Dr. Akst received funding from KayPentax and Olympus, both of which are not related to this work. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Address requests for reprints to: Martin B. Brodsky, PhD, ScM, Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, 600 N. Wolfe St., Phipps 181, Baltimore, MD 21287. E-mail: mbbrodsky@jhmi.edu

DOI: 10.1097/CCM.0000000000003368

extubation (2–4). Laryngeal injuries from intubation during surgery are believed to be confined to minor injuries (5–7). By comparison, critically ill patients intubated in ICU generally experience longer intubation resulting in laryngeal injuries that are more prevalent, potentially more severe, frequently overlooked, and often result in voice dysfunction (i.e., dysphonia) and/or swallowing dysfunction (i.e., dysphagia) (8–15). Despite potentially serious injury, laryngeal evaluations are often delayed, occurring only if symptoms persist greater than or equal to 1 week (4, 16, 17), sometimes as long as 1–3 months (18–20). This delay results, in part, from the absence of guidelines establishing standard practices for postextubation assessment. Patients with these injuries, therefore, experience increased risk for both medical sequelae (e.g., postintubation stenosis with delayed presentation [21, 22]) and prolonged functional handicap (e.g., chronic dysphonia [23], chronic dysphagia [24]).

The purposes of this systematic review are to 1) evaluate the nature and severity of laryngeal injury after endotracheal intubation in ICU patients and 2) identify areas of inquiry for mitigation strategies and future intervention. We focused on prospective studies with postextubation laryngoscopic assessment of laryngeal injury.

MATERIALS AND METHODS

Literature Search

A clinical informationist (C.P.) developed and executed the search strategy in the electronic bibliographic databases PubMed, Embase, CINAHL, and Cochrane Library from inception to April 2016, with two updates in March 2017 and September 2017 (**eAppendix 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D871). The searches were limited to the English language and created using controlled vocabulary, such as Medical Subject Headings, Emtree terms, and CINAHL headings, in combination with Key Words for the concepts of intubation, visualization techniques, and injury where appropriate. Efforts were made to exclude pediatric-focused research by excluding specific pediatric-related terms from the titles only, and a filter was applied to exclude animal-only research. A research filter was applied based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE, sensitivity, and precision-maximizing version (25) with additions for other types of clinical studies.

Selection Criteria

Included studies assessed adult (≥ 18 yr old) patients employing either direct (e.g., line of sight) or indirect (e.g., mirror, flexible endoscopy) visualization of the larynx and reported sufficient laryngeal injury data (e.g., frequencies, nature). Exclusion criteria included 1) non-English language, 2) case studies and retrospective study designs, 3) patients less than 18 years old, 4) preexisting laryngeal injury/disease, 5) patients with surgical interventions that have inherent risk of recurrent laryngeal nerve injury (e.g., neck surgeries, thoracic surgeries), 6) gray literature (26), and 7) nonfocal, neurologically impaired patient populations in whom neurologic injury may have made assignment of postintubation dysphonia and dysphagia to laryngeal injury difficult (e.g., stroke).

Data Extraction/Risk of Bias Assessment

Search strategy results were imported to an online platform (Covidence: www.covidence.org, Melbourne, VIC, Australia) for independent review. Two authors (E.J., B.B.) independently screened articles by title, abstract, and full text. Disagreements were refereed by a third author (M.B.B.). Six authors (M.B.B., M.J.L., E.J., V.P., G.C., L.M.A.) completed independent, double-data extraction, and risk of bias assessment for accepted articles. Risk of bias assessment followed the Cochrane Collaboration's criteria (27), with each risk variable judged as "low-, unknown-, or high- risk." Disagreements were settled by consensus. Authors were contacted to provide missing information as needed. A meta-analysis was judged to be inappropriate due to substantial heterogeneity of study methods for the accepted articles (28, 29).

A four-point grading rubric was used to classify laryngeal injuries, guided by previous publications (14, 30, 31). The rubric was developed via consensus by five authors: three laryngologists (A.T.H., S.R.B., L.M.A.), an emergency physician (M.J.L.), and a speech-language pathologist (M.B.B.). Prevalence was calculated as the total number of patients observed with each injury or symptom divided by the total number of patients analyzed across studies analyzing these outcomes, omitting studies that did not analyze a particular outcome and patients that did not meet criteria. All outcomes were assessed post extubation. Across studies, terminology describing voice quality was inconsistent. For purposes of prevalence, we report "dysphonia" and "hoarseness" separately using the terms relevant to each article, but we group these symptoms of laryngeal injury as "voice dysfunction" in our discussion.

RESULTS

Search Results

There were 4,530 publications identified from the four databases and other sources as part of a larger systematic review on laryngeal injury. Screening by title and abstract resulted in 126 full-text reviews. Of these, nine studies from five countries were accepted with the focus on laryngeal injury from oral endotracheal intubation in mechanically ventilated ICU patients (**Fig. 1**). These nine studies comprised seven cohort studies (663 patients) (32–38) and two cross-sectional studies (112 patients) (39, 40), totaling 775 patients (**Table 1**).

Clinical Presentation

Eight studies had laryngeal injury after oral intubation as the primary objective (33–36, 39), whereas one study had frequency of dysphagia post extubation as its primary objective (40). Patients' mean (SD; 95% CI) age was 53.4 years (7.0 yr; 52.8–54.0 yr) across the eight studies (89%) reporting age (32–37, 39, 40). Diagnoses included cardiac (37, 40), medical (32, 33, 35, 37–40), mixed medical-surgical (39), oncological

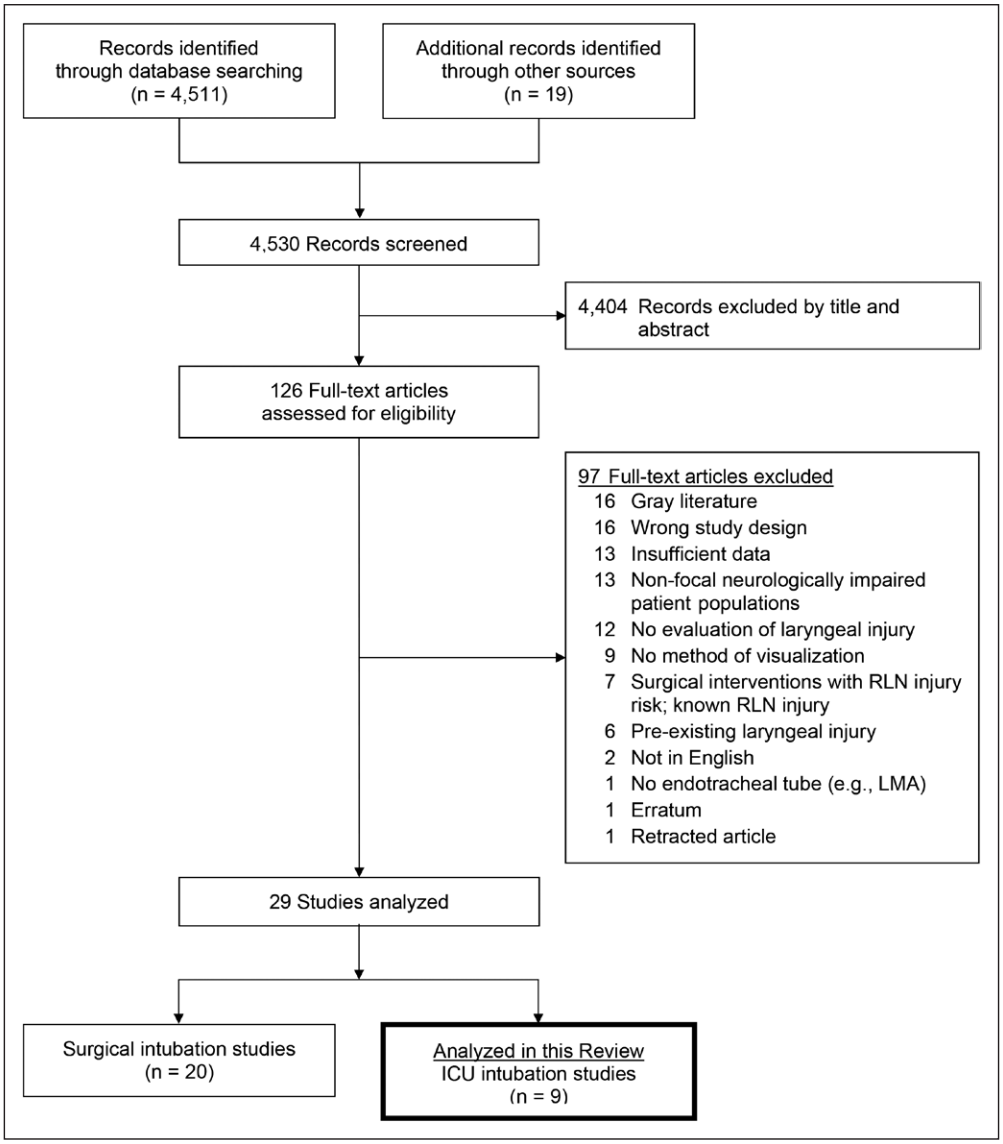

Figure 1. Study selection flowchart. LMA = laryngeal mask airway, RLN = recurrent laryngeal nerve.

(37, 40), surgical (38–40), nonneurologic trauma (40), and unclear/unstated diagnoses (34, 36, 40). Whereas six studies (67%) reported endotracheal tube (ETT) size (32–35, 39, 40), only one study (11%) distinguished ETT size between the sexes, with most females receiving a 7.0 mm inner diameter (range, 6.5–7.0 mm) compared with most males receiving an 8.0 mm inner diameter (range, 7.5–8 mm) (33). Two studies (22%) reported ETT manufacturer (32, 35). Across seven studies (78%), the calculated mean (SD; 95% CI) duration of intubation was 8.2 days (6.0 d; 7.7–8.7 d) (32, 33, 35–37, 39, 40). One study (11%) reported median duration of 4 days, but without any measure of variability (34) and one study reported three groups with ranges of intubation duration without summary statistics (38) (Table 1).

Assessment and Diagnosis

Direct visualization via laryngoscope (37, 38) was used in two studies (22%). Indirect visualization as a laryngeal mirror (38), rigid endoscope (34) flexible nasoendoscopy (33, 35, 36, 38–40), and flexible bronchoscopy was used in eight studies (89%) (Table 1) (32). Otolaryngologist interpretation of findings was confirmed in seven studies (78%) (33–35, 39–40). After extubation, assessment was completed within 6 hours (35–37), within 24 hours (33, 34, 38, 39), within 72 hours (40), and at 2 weeks post extubation (32).

Laryngeal Injury–Signs

The prevalence of postextubation laryngeal injury across all four severity grades is summarized in **Table 2**. Injuries were inconsistently reported across studies, as seen in the raw data presented in **Supplementary Table 1** (Supplemental Digital Content 2, http://links.lww.com/CCM/D872). No laryngeal injury was observed in 17% of patients across the seven studies (78%) reporting this outcome (32–35, 37, 39, 40).

A high prevalence of minor injury and lower prevalence of more severe injury occurred. Many injuries were self-limiting, grade 1 injuries. Overall, erythema was most frequent, with a prevalence of 82% (252/307 patients) (34, 36, 39, 40), followed closely by edema with a prevalence of 70% (583/828 patients) (33–36, 39, 40). The interarytenoid space, the area through which the ETT passes and remains present in situ, had a 95% (106/112 patients) and 96% (108/112 patients) prevalence of edema and erythema, respectively (39, 40). Ulcerations, with a 31% prevalence (174/524 patients), were the most frequently reported moderate (i.e., grade 2) injury (32, 33, 35–37, 39, 40). Intubation granulomas/granulation tissue, the only other injury type reported, had a 27% prevalence (86/318 patients) (32, 34, 35, 39, 40). Vocal fold immobility was the most frequently reported and most common of the severe (i.e., grade 3) injuries, with a 21% prevalence (105/508 patients) (32, 33, 35, 36, 39, 40). There was a 6% prevalence (12/200 patients) of glottic stenosis (38) and 13% prevalence (15/112 patients) of subglottic stenosis (39, 40). A prevalence of 5% or less for both subglottic mucosa edema (32) and arytenoid(s) dislocation were reported (33).

TABLE 1. Methods of Included Studies

References	Country	Study Design	Number of Patients Analyzed[a]	Mean Patient Age (yr)	Endotracheal Tube Size	Method of Visualization	Duration of Intubation (Mean Days)
Colton House et al (39)	United States	Cross-sectional	61	56	6.0–8.0	Indirect	9
Kastanos et al (32)	Spain	Cohort	19	59	7.0–9.0	Indirect	6.2
Megarbane et al (33)	France	Cohort	209	40	6.5–8.0	Indirect	1.2
Rangachari et al (34)	India	Cohort	51	50	7.0–8.5	Indirect	4[b]
Scheel et al (40)	United States	Cross-sectional	51	58	≤ 7, ≥ 8	Indirect	9.4
Tadié et al (35)	France	Cohort	136	62	6.5–8.0	Indirect	6.9
Van der Meer et al (36)	South Africa	Cohort	32	49	NR	Indirect	4.5
Volpi et al (37)	United States	Cohort	16	53	NR	Direct	20.3
Whited (38)	United States	Cohort	200	NR	NR	Direct, indirect	NR

NR = not reported.
[a]Reflects the number of patients meeting inclusion/exclusion criteria and therefore analyzed and reported in this systematic review.
[b]Duration in median days.

TABLE 2. Prevalence of Laryngeal Injury Grade by Average Intubation Duration

Injury Grade	All Patients, *N*[a] = 775 (32–40), *n*[b] (%)	Average Intubation Duration		
		< 5 d, *N*[a] = 342 (33, 34, 36, 38), *n*[b] (%)	5–10 d, *N*[a] = 367 (32, 35, 38–40), *n*[b] (%)	> 10 d, *N*[a] = 66 (37, 38), *n*[b] (%)
0—No injury present	94/543 (17) (32–35, 37, 39, 40)	52/260 (20) (33, 34)	42/267 (16) (32, 35, 39, 40)	0/16 (0) (37)
1—Self-limited, soft tissue (e.g., edema, erythema, hyperplasia, ecchymosis)	835/1,135 (74) (33–36, 39, 40)	265/439 (60) (33, 34, 36)	570/696 (82) (35, 39, 40)	—
2—Hematoma, ulceration, fibrin without glottic narrowing, mass lesion, granulation	260/842 (31) (32–37, 39, 40)	70/292 (24) (33, 34, 36)	174/534 (33) (32, 35, 39, 40)	16/16 (100) (37)
3—Stenosis, stenosis with glottic narrowing, hypomobility/immobility of the vocal folds and/or arytenoids complex	137/1,048 (13) (32, 33, 35, 36, 38–40)	39/500 (8) (33, 36, 38)	90/498 (18) (32, 35, 38–40)	7/50 (14) (38)

[a]*N*: The total number of subjects across studies.
[b]*n*: The total number of occurrences observed with each injury and within each injury grade divided by the number of possible occurrences. The number of possible occurrences was calculated as the product number of patients evaluated and the number of types of injuries evaluated for each study. Note that each study may not report all injury types. For example, the prevalence of a grade 1 injury considers all possible injury types (e.g., edema, erythema, hyperplasia, ecchymosis). In the "All Patients" column, the studies reporting each injury type observed 835 occurrences of grade 1 injury types across 1,135 possibilities that they could have occurred or 74% prevalence of grade 1 injury.

Laryngeal injury prevalence may change with longer durations of intubation. We further analyzed injury findings based on three average durations of intubation identified by data generated from this review: 1) less than 5 days (33, 34, 36), 2) 5–10 days (32, 35, 39, 40), and 3) greater than 10 days (37, 38) (Table 2; and **Supplementary Table 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/D873). There was increased prevalence and increased severity of injury observed in patients intubated 5–10 days compared with those intubated less than 5 days. Specifically, there was a 37% and 38% increased prevalence of injury in grades 1 and 2, respectively. Grade 3 had a 125% increase in prevalence between the same two periods. Two studies with durations greater than 10 days (37, 38) reported three unique injury types and are unable to be summarized.

Delays in postextubation assessment may also contribute to variability in laryngeal injury prevalence. We identified four windows of assessment across studies: 1) less than or equal to 6 hours (35–37), 2) less than or equal to 24 hours (33, 34, 38, 39), 3) less than or equal to 72 hours (40), and 4) 2 weeks (32) (**Table 3**; and **Supplementary Table 3**, Supplemental Digital Content 4, http://links.lww.com/CCM/D874). Compared with overall prevalence and considering variability in the reporting of data, timing of assessment resulted in little change in laryngeal injury prevalence within grade. This finding suggests that the injuries observed vary little within 3 days post extubation.

TABLE 3. Prevalence of Laryngeal Injury Grade by Timing of Assessment Post Extubation

Injury Grade	Timing of Assessment Post Extubation			
	≤ 6 hr, *N*[a] = 184 (35–37), *n*[b] (%)	≤ 24 hr, *N*[a] = 521 (33, 34, 38, 39), *n*[b] (%)	≤ 72 hr, *N*[a] = 51 (40), *n*[b] (%)	2 wk, *N*[a] = 19 (32), *n*[b] (%)
0—No injury present	36/152 (24) (35, 37)	52/321 (16) (33, 34, 39)	3/51 (6) (40)	3/19 (16) (32)
1—Self-limited, soft tissue (e.g., edema, erythema, hyperplasia, ecchymosis)	167/264 (63) (35, 36)	441/616 (72) (33, 34, 39)	227/255 (89) (40)	–
2—Hematoma, ulceration, fibrin without glottic narrowing, mass lesion, granulation	77/320 (24) (35–37)	122/382 (32) (33, 34, 39)	46/102 (45) (40)	15/38 (39) (32)
3—Stenosis, stenosis with glottic narrowing, hypomobility/immobility of the vocal folds and/or arytenoids complex	30/168 (18) (35, 36)	79/740 (11) (33, 38, 39)	26/102 (25) (40)	2/38 (5) (32)

[a]*N*: The total number of subjects across studies.

[b]*n*: The total number of occurrences observed with each injury and within each injury grade divided by the number of possible occurrences. The number of possible occurrences was calculated as the product number of patients evaluated and the number of types of injuries evaluated for each study. Note that each study may not report all injury types. For example, the prevalence of a grade 1 injury considers all possible injury types (e.g., edema, erythema, hyperplasia, ecchymosis). In the "All Patients" column, the studies reporting each injury type observed 835 occurrences of grade 1 injury types across 1,135 possibilities that they could have occurred or 74% prevalence of grade 1 injury.

One study completed assessments 2 weeks post extubation and demonstrated 84% prevalence of injury in patients who were intubated a mean of 6.2 days (range, 2–14 d), similar to each of the earlier time points (32).

Laryngeal Injury–Symptoms

Symptoms of laryngeal injury identified after extubation were common (**Table 4**; Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/CCM/D872; Supplemental Table 2, Supplemental Digital Content 3, http://links.lww.com/CCM/D873; and Supplemental Table 3, Supplemental Digital Content 4, http://links.lww.com/CCM/D874), with voice dysfunction (i.e., dysphonia), dysphagia, and pain being the most frequent. Both voice dysfunction (197/260 patients) (32, 33, 36) and pain (184/241 patients) (33, 36) had a 76% prevalence. Dysphagia had a prevalence of 49% (157/319 patients) (32, 33, 36, 40). Laryngeal dyspnea and stridor were least frequent with a prevalence of 23% (48/209 patients) (33) and 7% (11/155 patients) (32, 35), respectively.

Methodological Quality

Methodological quality is summarized as risk of bias (**Supplementary Table 4**, Supplemental Digital Content 5, http://links.lww.com/CCM/D875). All studies provided adequate rationale with clear objectives. Most studies included sufficient subject selection criteria (8/9; 89%) and minimized reporting bias (7/9; 78%). Weaknesses included insufficient information for study replication (3/9; 33%) and appropriate controls for sampling (3/9; 67%), in addition to detection (5/9; 56%), attrition (3/9; 33%), and avoidance (3/9; 33%) biases.

DISCUSSION

This systematic review demonstrates that laryngeal injury is a frequent consequence of intubation and is exacerbated with increased duration, despite considerable variability of study methods, patient populations, and outcomes reporting among the accepted articles. Only a small fraction of patients will emerge from intubation injury free. Although less severe injuries are more common, grades 2 and grade 3 injuries occur with a remarkable frequency of 31% and 13%, respectively. On average, more than twice as many patients will sustain moderate or severe injuries that impact airway, voice, and/or swallowing than will have no injury. Assessments completed within 72 hours of extubation appear to have little effect on outcomes, suggesting that resolution of even less severe injuries extends beyond 3 days.

A necessary first step in managing laryngeal injuries is in determining their presence and severity to facilitate appropriate and individualized management. Management could be coordinated by the ICU team and involve a variety of other disciplines. Treatment might include prescribing glucocorticoids (41) and anti-reflux medications (42), procedures such as stenosis dilation (43) and vocal fold medialization by anesthesiology and otolaryngology (44, 45), therapy by speech-language pathology for voice (46, 47) and swallowing (48, 49), and other complementary therapies for improving patient function and quality of life (50, 51).

One finding worth highlighting is that approximately half of all patients experienced dysphagia after extubation and that one in five patients had vocal fold immobility. It is well-recognized that intubation duration more than 2 days places patients at high risk for both acute and chronic dysphagia (24, 33, 40, 52, 53) that may result in aspiration, possibly leading to aspiration pneumonia or pneumonitis (54–58). There are several potential contributing etiologies that might increase aspiration risk in this population, including compromised cognition (59), sensory impairment (4, 60), reduced laryngeal adductor reflex (61, 62), and reduced strength in muscles involved in swallowing (63). Emerging evidence is linking morphological laryngeal injury to aspiration (40), with an aspiration prevalence of

TABLE 4. Prevalence of Symptoms Reported Post Extubation

Symptoms	Patients, *n*[a] (%)
Dysphonia (including hoarseness)	197/260 (76) (32, 33, 36)
Pain	184/241 (76) (33, 36)
Dysphagia	157/319 (49) (32, 33, 36, 40)
Laryngeal dyspnea	48/209 (23) (33)
Stridor	11/155 (7) (32, 35)
Overall	597/1,184 (50) (32, 33, 35, 36, 40)

[a]Prevalence is reported as the total number observed divided by the total number of patients analyzed for each sign/symptom across studies.

38–44% during oral consumption in patients with unilateral vocal fold immobility (64, 65). Furthermore, the risk of pneumonia doubles in patients with unilateral vocal fold paralysis (66). Early recognition of vocal fold paralysis may mitigate risks for pneumonia or pneumonitis with a timely vocal fold medialization procedure, for example (44, 67). Additionally, comprehensive investigation may identify other findings associated with symptoms such as dysphagia, increasing the chances for earlier risk stratification and appropriate management.

Similar ETT inner diameters (i.e., ETT size) were used across studies, but not all studies reported size and/or manufacturer. This presents two issues for attribution of laryngeal injury to ETT size. First, there is no standard for assigning ETT size, but size: 1) reflects "inner" lumen diameter, 2) has no association with "outer" diameter measurement, 3) is similar across manufacturers, and 4) may be considered with therapeutic value (e.g., air volume, pressure, oxygenation) (68) and instruments use via the ETT (e.g., bronchoscope). The ETT outer diameter: 1) contacts anatomical structures, 2) is associated with occupying space within the larynx/trachea, and 3) is, at least partly, responsible for laryngeal injuries and their symptoms. There is minor (≤ 0.5 mm) variability in outer diameter between manufacturers (i.e., Mallinckrodt, Staines-upon-Thames, United Kingdom; Portex, Minneapolis, MN; Smiths Medical, Minneapolis, MN; Unomedical: Kedah, Malaysia), each using similar materials. However, Mallinckrodt currently produces two ETTs (i.e., TaperGuard Evac, SealGuard Evac) that have outer diameters approximately 1 mm larger than other ETTs across sizes and manufacturers (69). No conclusions can be made concerning laryngeal injury, ETT size, and/or materials/manufacturing due to the large variability within and between studies. Future studies should report these characteristics to address this concern.

Our findings encourage more routine, timely and consistent use of a laryngeal assessment and dysphagia screening post extubation, especially in the wake of payment reform and a national focus on patient safety. Hospital-acquired conditions represent a multidimensional risk with both cost and exposure dimensions. Aspiration pneumonia and pneumonitis are potentially preventable hospital-acquired conditions that require significant resources, including primary care and specialty physicians (70), with prevalence as high as 14% in postextubated ICU patient populations (53). Hospital-acquired pneumonia can increase length of stay in the ICU by more than 8 days (71). The exposure and costs (financially and in occupancy) associated with such preventable harm represent a strong market, fiscal, and moral case for prevention, or at least early screening, assessment, and treatment. A screening for laryngeal injury is, perhaps, more complicated. Moderate to severe laryngeal injuries may result in more than 2 days and $6,000 in costs with readmission for repair (72). Despite frequent complaints of dysphonia and pain after extubation, identifying which patients are at high risk for moderate to severe laryngeal injury and the best time for assessment is less clear. Furthermore, there are no screening tools or published guidelines offering direction on this issue, a large gap in critical care patient populations and their long-term outcomes (73).

Regardless of which symptom(s) are present, "wait and see" remains the most common approach to identification and management of these injuries (4–18), despite nearly 40 years of evidence and recommendations for more timely evaluations (15, 32, 33, 40, 74, 75). Remarkably, there are no published guidelines for postextubation assessment of laryngeal injury or dysphagia. The only published guideline concerning postextubation assessment specifically addresses one symptom—hoarseness (20). It states that the laryngoscopic evaluation of patients with both hoarseness and a history of intubation "may [be completed] at any time" (p. S14), but "clinicians should perform laryngoscopy… [with unresolved hoarseness] within 4 weeks or irrespective of duration if a serious underlying cause is suspected" (p. S15) (20). Much is left to interpretation from these recommendations because they are made for hoarseness of any etiology, written for ambulatory outpatients instead of at-risk ICU patients, and are not specific to intubation injury. We emphasize that hoarseness may be only one of many symptoms of laryngeal injury. Among the most prevalent symptoms is pain, which may be indicative of serious laryngeal injury. Dysphagia is also highly prevalent with potential for serious consequences soon after extubation (8, 32, 33, 35, 36, 40). Future studies and screening guidelines should consider these other symptoms.

A high risk of bias was observed in greater than 50% of the rating variables. These results appear to reflect difficulties controlling experimenter biases, specifically: 1) detection bias and 2) attrition bias, avoidance bias, and reporting bias. The two cross-sectional studies (both from one laboratory) included in this review represent a low risk of bias across all variables (39, 40). The seven cohort studies all introduced unknown or high risks of bias (32–38). The introduction of these biases may reflect the dynamic, frequently unpredictable ICU setting combined with data collection across multiple time points. Extra care must be taken to reduce biases through methodological controls with these types of study designs. Clarity in writing for study replication is also concerning. Editorial review and publication guidelines for clinical studies should strive for improvements in writing clarity and reduction of study biases.

There are three potential limitations noted. First, our search was limited to the English language. We acknowledge that

studies from other languages may provide results that are contrary to our findings and conclusions, but we believe this to be unlikely with the robust agreement between studies accepted for review. Second, our data were limited to ICU. Intubation is also performed routinely in emergency medicine and surgical settings. Although emergency medicine settings were not specifically excluded, we are not aware of any studies using laryngoscopy for postextubation evaluation of these patients. Studies about intubation trauma and laryngeal injury in surgical settings offer a different patient population and considerable differences in intubation duration and were not the focus of this review. Third, after study acceptance, we observed a greater than or equal to 19-year gap between three studies published in/before 1987 (32, 37, 38) and the next study published in 2006 (34). Although clinical practice and improved construction of ETTs during this period may have impacted intubation technique and laryngeal injury, prevalence of injury between these two time periods were similar. Despite these limitations, this systematic review makes a novel contribution toward ongoing research in the area of postextubation laryngeal injury and is a call to action for increased awareness of this phenomenon.

CONCLUSIONS

Considering the prevalence of laryngeal injury, dysphonia, and dysphagia and their associated risks for more serious medical complications, practice guidelines are needed for postextubation screening/assessment in the ICU. Evidence strongly indicates that intubation duration is associated with prevalence and severity of laryngeal injuries. Injuries are frequent and range widely in severity post extubation. Although mild injuries are more prevalent, moderate to severe injuries occur frequently and require timely clinical attention. Presently, no clinical standards of practice address these potentially serious injuries, and there is little evidence in this review to offer direction. Findings suggest new areas for scientific inquiry and highlight long-known and under-identified iatrogenic injury from one of the most common procedures in medicine—endotracheal intubation.

REFERENCES

1. Adhikari NK, Fowler RA, Bhagwanjee S, et al: Critical care and the global burden of critical illness in adults. *Lancet* 2010; 376:1339–1346
2. Bishop MJ, Weymuller EA Jr, Fink BR: Laryngeal effects of prolonged intubation. *Anesth Analg* 1984; 63:335–342
3. Santos PM, Afrassiabi A, Weymuller EA Jr: Prospective studies evaluating the standard endotracheal tube and a prototype endotracheal tube. *Ann Otol Rhinol Laryngol* 1989; 98:935–940
4. Benjamin B, Holinger LD: Laryngeal complications of endotracheal intubation. *Ann Otol Rhinol Laryngol* 2008; 117(9 Suppl 200):2–20
5. Alexopoulos C, Lindholm CE: Airway complaints and laryngeal pathology after intubation with an anatomically shaped endotracheal tube. *Acta Anaesthesiol Scand* 1983; 27:339–344
6. Nordang L, Lindholm CE, Larsson J, et al: Early laryngeal outcome of prolonged intubation using an anatomical tube: A double blind, randomised study. *Eur Arch Otorhinolaryngol* 2016; 273:703–708
7. Geraci G, Cupido F, Lo Nigro C, et al: Postoperative laryngeal symptoms in a general surgery setting. Clinical study. *Ann Ital Chir* 2013; 84:377–383
8. Donnelly WH: Histopathology of endotracheal intubation. An autopsy study of 99 cases. *Arch Pathol* 1969; 88:511–520
9. Dubick MN, Wright BD: Comparison of laryngeal pathology following long-term oral and nasal endotracheal intubations. *Anesth Analg* 1978; 57:663–668
10. Brandwein M, Abramson AL, Shikowitz MJ: Bilateral vocal cord paralysis following endotracheal intubation. *Arch Otolaryngol Head Neck Surg* 1986; 112:877–882
11. Colice GL, Stukel TA, Dain B: Laryngeal complications of prolonged intubation. *Chest* 1989; 96:877–884
12. Santos PM, Afrassiabi A, Weymuller EA Jr: Risk factors associated with prolonged intubation and laryngeal injury. *Otolaryngol Head Neck Surg* 1994; 111:453–459
13. Massard G, Rougé C, Dabbagh A, et al: Tracheobronchial lacerations after intubation and tracheostomy. *Ann Thorac Surg* 1996; 61:1483–1487
14. Eckerbom B, Lindholm CE, Alexopoulos C: Airway lesions caused by prolonged intubation with standard and with anatomically shaped tracheal tubes. A post-mortem study. *Acta Anaesthesiol Scand* 1986; 30:366–373
15. Brodsky MB, González-Fernández M, Mendez-Tellez PA, et al: Factors associated with swallowing assessment after oral endotracheal intubation and mechanical ventilation for acute lung injury. *Ann Am Thorac Soc* 2014; 11:1545–1552
16. Benjamin B: Prolonged intubation injuries of the larynx: Endoscopic diagnosis, classification, and treatment. *Ann Otol Rhinol Laryngol Suppl* 1993; 160:1–15
17. Sadoughi B, Fried MP, Sulica L, et al: Hoarseness evaluation: A transatlantic survey of laryngeal experts. *Laryngoscope* 2014; 124:221–226
18. Colice GL: Resolution of laryngeal injury following translaryngeal intubation. *Am Rev Respir Dis* 1992; 145:361–364
19. Schwartz SR, Cohen SM, Dailey SH, et al: Clinical practice guideline: Hoarseness (dysphonia). *Otolaryngol Head Neck Surg* 2009; 141(3 Suppl 2):S1–S31
20. Stachler RJ, Francis DO, Schwartz SR, et al: Clinical practice guideline: hoarseness (dysphonia) (update). *Otolaryngol Head Neck Surg* 2018; 158(1_Suppl):S1–S42
21. Whited RE: A prospective study of laryngotracheal sequelae in long-term intubation. *Laryngoscope* 1984; 94:367–377
22. Wain JC: Postintubation tracheal stenosis. *Chest Surg Clin N Am* 2003; 13:231–246
23. Havas TE, Priestley J, Lowinger DS: A management strategy for vocal process granulomas. *Laryngoscope* 1999; 109:301–306
24. Brodsky MB, Huang M, Shanholtz C, et al: Recovery from dysphagia symptoms after oral endotracheal intubation in acute respiratory distress syndrome survivors. A 5-year longitudinal study. *Ann Am Thorac Soc* 2017; 14:376–383
25. Higgins JPT, Green S (Eds): Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.
26. Alberani V, De Castro Pietrangeli P, Mazza AM: The use of grey literature in health sciences: A preliminary survey. *Bull Med Libr Assoc* 1990; 78:358–363
27. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group: The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928
28. Borenstein M, Hedges LV, Higgins JP, et al: A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010; 1:97–111
29. Møller AM, Myles PS: What makes a good systematic review and meta-analysis? *Br J Anaesth* 2016; 117:428–430
30. Lindholm C-E: Prolonged Endotracheal Intubation: A clinical investigation with special reference to its consequences for the larynx and trachea and to its place an alternative to intubation through a tracheostomy. *Acta Anaesthesiol Scand* 1969; 13:1–80
31. Thomas R, Kumar EV, Kameswaran M, et al: Post intubation laryngeal sequelae in an intensive care unit. *J Laryngol Otol* 1995; 109:313–316

32. Kastanos N, Estopá Miró R, Marín Perez A, et al: Laryngotracheal injury due to endotracheal intubation: Incidence, evolution, and predisposing factors. A prospective long-term study. *Crit Care Med* 1983; 11:362–367
33. Megarbane B, Be Hong T, Kania R, et al: Early laryngeal injury and complications because of endotracheal intubation in acutely poisoned patients: A prospective observational study. *Clin Toxicol (Phila)* 2010; 48:331–336
34. Rangachari V, Sundararajan I, Sumathi V, et al: Laryngeal sequelae following prolonged intubation: A prospective study. *Indian J Crit Care Med* 2006; 10:171–175
35. Tadié JM, Behm E, Lecuyer L, et al: Post-intubation laryngeal injuries and extubation failure: A fiberoptic endoscopic study. *Intensive Care Med* 2010; 36:991–998
36. Van der Meer G, Ferreira Y, Loock JW: The S/Z ratio: A simple and reliable clinical method of evaluating laryngeal function in patients after intubation. *J Crit Care* 2010; 25:489–492
37. Volpi D, Lin PT, Kuriloff DB, et al: Risk factors for intubation injury of the larynx. *Ann Otol Rhinol Laryngol* 1987; 96:684–686
38. Whited RE: Posterior commissure stenosis post long-term intubation. *Laryngoscope* 1983; 93:1314–1318
39. Colton House J, Noordzij JP, Murgia B, et al: Laryngeal injury from prolonged intubation: A prospective analysis of contributing factors. *Laryngoscope* 2011; 121:596–600
40. Scheel R, Pisegna JM, McNally E, et al: Endoscopic assessment of swallowing after prolonged intubation in the ICU setting. *Ann Otol Rhinol Laryngol* 2016; 125:43–52
41. Rafii B, Sridharan S, Taliercio S, et al: Glucocorticoids in laryngology: A review. *Laryngoscope* 2014; 124:1668–1673
42. Hanson DG, Kamel PL, Kahrilas PJ: Outcomes of antireflux therapy for the treatment of chronic laryngitis. *Ann Otol Rhinol Laryngol* 1995; 104:550–555
43. Hillel AT, Karatayli-Ozgursoy S, Benke JR, et al: Voice quality in laryngotracheal stenosis: Impact of dilation and level of stenosis. *Ann Otol Rhinol Laryngol* 2015; 124:413–418
44. Bhattacharyya N, Kotz T, Shapiro J: Dysphagia and aspiration with unilateral vocal cord immobility: Incidence, characterization, and response to surgical treatment. *Ann Otol Rhinol Laryngol* 2002; 111:672–679
45. Rosero EB, Ozayar E, Mau T, et al: A sequential anesthesia technique for surgical repair of unilateral vocal fold paralysis. *J Anesth* 2016; 30:1078–1081
46. American Speech-Language-Hearing Association: The Use of Voice Therapy in the Treatment of Dysphonia [Technical Report], 2005. Available at: https://www.asha.org/policy/tr2005-00158. Accessed May 27, 2018
47. Angadi V, Croake D, Stemple J: Effects of vocal function exercises: A systematic review. *J Voice* 2017 Nov 3. [Epub ahead of print]
48. Langmore SE: History of fiberoptic endoscopic evaluation of swallowing for evaluation and management of pharyngeal dysphagia: Changes over the years. *Dysphagia* 2017; 32:27–38
49. Macht M, White SD, Moss M: Swallowing dysfunction after critical illness. *Chest* 2014; 146:1681–1689
50. Cardoso R, Meneses RF, Lumini-Oliveira J: The effectiveness of physiotherapy and complementary therapies on voice disorders: A systematic review of randomized controlled trials. *Front Med (Lausanne)* 2017; 4:45
51. Rohof WO, Myers JC, Estremera FA, et al: Inter- and intra-rater reproducibility of automated and integrated pressure-flow analysis of esophageal pressure-impedance recordings. *Neurogastroenterol Motil* 2014; 26:168–175
52. Brodsky MB, Gellar JE, Dinglas VD, et al: Duration of oral endotracheal intubation is associated with dysphagia symptoms in acute lung injury patients. *J Crit Care* 2014; 29:574–579
53. Macht M, Wimbish T, Clark BJ, et al: Postextubation dysphagia is persistent and associated with poor outcomes in survivors of critical illness. *Crit Care* 2011; 15:R231
54. Kozlow JH, Berenholtz SM, Garrett E, et al: Epidemiology and impact of aspiration pneumonia in patients undergoing surgery in Maryland, 1999-2000. *Crit Care Med* 2003; 31:1930–1937
55. Marik PE: Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med* 2001; 344:665–671
56. Skoretz SA, Flowers HL, Martino R: The incidence of dysphagia following endotracheal intubation: A systematic review. *Chest* 2010; 137:665–673
57. Schmidt J, Holas M, Halvorson K, et al: Videofluoroscopic evidence of aspiration predicts pneumonia and death but not dehydration following stroke. *Dysphagia* 1994; 9:7–11
58. Macht M, Wimbish T, Bodine C, et al: ICU-acquired swallowing disorders. *Crit Care Med* 2013; 41:2396–2405
59. Leder SB, Suiter DM, Lisitano Warner H: Answering orientation questions and following single-step verbal commands: Effect on aspiration status. *Dysphagia* 2009; 24:290–295
60. Aucott W, Prinsley P, Madden G: Laryngeal anaesthesia with aspiration following intubation. *Anaesthesia* 1989; 44:230–231
61. Kaneoka A, Pisegna JM, Inokuchi H, et al: Relationship between laryngeal sensory deficits, aspiration, and pneumonia in patients with dysphagia. *Dysphagia* 2018; 33:192–199
62. Kaneoka A, Pisegna JM, Krisciunas GP, et al: Variability of the pressure measurements exerted by the tip of laryngoscope during laryngeal sensory testing: A clinical demonstration. *Am J Speech Lang Pathol* 2017; 26:729–736
63. Brodsky MB, De I, Chilukuri K, et al: Coordination of pharyngeal and laryngeal swallowing events during single liquid swallows after oral endotracheal intubation for patients with acute respiratory distress syndrome. *Dysphagia* 2018 Apr 30. [Epub ahead of print]
64. Leder SB, Ross DA: Incidence of vocal fold immobility in patients with dysphagia. *Dysphagia* 2005; 20:163–167; discussion 168–169
65. Domer AS, Leonard R, Belafsky PC: Pharyngeal weakness and upper esophageal sphincter opening in patients with unilateral vocal fold immobility. *Laryngoscope* 2014; 124:2371–2374
66. Tsai MS, Yang YH, Liu CY, et al: Unilateral vocal fold paralysis and risk of pneumonia: A nationwide population-based cohort study. *Otolaryngol Head Neck Surg* 2018; 158:896–903
67. Cates DJ, Venkatesan NN, Strong B, et al: Effect of vocal fold medialization on dysphagia in patients with unilateral vocal fold immobility. *Otolaryngol Head Neck Surg* 2016; 155:454–457
68. Stenqvist O, Sonander H, Nilsson K: Small endotracheal tubes: Ventilator and intratracheal pressures during controlled ventilation. *Br J Anaesth* 1979; 51:375–381
69. Covidien: Mallinckrodt™ Tracheal Tubes Airway Product Catalogue. Dublin, Republic of Ireland, Covidien, 2012
70. Centers for Medicare and Medicaid Services: Hospital Inpatient PPS for Acute Care Hospitals and the Long-Term Care Hospital PPS & FY 2015 Rates. Health and Human Services, 2014. CMS-1607-F. Available at: http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalAcqCond/HAC-Regulations-and-Notices-Items/CMS-1607-F.html. Accessed October 1, 2018
71. Zimlichman E, Henderson D, Tamir O, et al: Health care-associated infections: A meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med* 2013; 173:2039–2046
72. Bhatti NI, Mohyuddin A, Reaven N, et al: Cost analysis of intubation-related tracheal injury using a national database. *Otolaryngol Head Neck Surg* 2010; 143:31–36
73. Needham DM, Davidson J, Cohen H, et al: Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference. *Crit Care Med*. 2012; 40:502–509
74. Kambic V, Radsel Z: Intubation lesions of the larynx. *Br J Anaesth* 1978; 50:587–590
75. Gallivan GJ, Dawson JA, Robbins LD: Critical care perspective: Videolaryngoscopy after endotracheal intubation: Implications for voice. *J Voice* 1989; 3:76–80