



<https://doi.org/10.1016/j.jemermed.2021.07.012>

## Original Contributions

### Emergency Department Intubations in Patients With Angioedema: A Report from the National Emergency Airway Registry

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**Abstract—Background:** Angioedema, a localized swelling of subcutaneous and submucosal tissues, may involve the upper airway. A subset of patients presenting for emergent evaluation of angioedema will require intubation. Little is known about airway management practices in patients with angioedema requiring intubation in the emergency department (ED). **Objective:** To describe airway management practices in patients intubated for angioedema in the ED. **Methods:** We analyzed data from the National Emergency Airway Registry. All patients with an intubation attempt for angioedema between January 1, 2016 and December 31, 2018 were included. We report univariate descriptive data as proportions with cluster-adjusted 95% confidence intervals. **Results:** Of 19,071 patient encounters, intubation was performed for angioedema in 98 (0.5%). First-attempt success was achieved in 81%, with emergency physicians performing the procedure in 94% of encounters. The most common device used was a flexible endoscope (49%), and 42% of attempts were via a nasal route. Pharmacologic methods included sedation with paralysis (61%), topical anesthesia with or without sedation (13% and 13%, respectively), and sedation only (10%). Among 19 (19%) patients requiring additional attempts, intubation was achieved on second at-

tempt in 10 (53%). The most common adverse events were hypotension (13%) and hypoxemia (12%). Cricothyrotomy occurred in 2 patients (2%). No deaths were observed.

**Conclusions:** Angioedema was a rare indication for intubation in the ED setting. Emergency physicians achieved first-attempt success in 81% of encounters and used a broad range of intubation devices and methods, including flexible endoscopic techniques. Cricothyrotomy was rare, and no ED deaths were reported. © 2021 Elsevier Inc. © 2021 Elsevier Inc. All rights reserved.

**Keywords—**angioedema; emergency department; endotracheal intubation

#### Introduction

Angioedema is a disorder resulting from bradykinin- or histamine-mediated immunologic responses. It is characterized by the acute onset of self-limited, localized, nonpitting swelling of the subcutaneous or submucosal tissues. Angioedema represents approximately 1 of every 1000 emergency department (ED) visits, or 117,000 ED visits annually in the United States (1).

Reprints are not available from the authors.

RECEIVED: 18 March 2021; FINAL SUBMISSION RECEIVED: 3 May 2021;  
 ACCEPTED: 3 July 2021

Life-threatening airway obstruction can occur when angioedema involves the structures of the upper airway (2,3). Although the overall mortality has been reported to be low, prompt identification and appropriate management during impending airway obstruction is vital, because asphyxiation represents the principal cause of death in this patient population (4).

Flexible endoscopic intubation has been advocated as the primary technique for managing the airway in patients with angioedema; however, this technique is rarely used in clinical practice (5). With advances in emergency airway management during the past 2 decades, particularly the adoption of video laryngoscopy, airway management strategies have evolved (6,7). Limited data exist on the success of airway maneuvers in patients with angioedema, and the current published literature is limited to single-center retrospective reviews (8,9). We sought to describe patient characteristics, emergency airway management techniques, and outcomes among patients in the ED who were enrolled in a multicenter prospective registry and were managed for angioedema.

## Materials and Methods

### *Study Design and Setting*

We analyzed data from the National Emergency Airway Registry (NEAR), a prospective multicenter registry of ED intubations performed at a network of U.S. academic EDs, from January 1, 2016 through December 31, 2018. The study dates were determined by the most recent iteration of NEAR, which ceased collection of data at the end of 2018. Data from previous iterations of NEAR were not included, because data collection forms varied from the present iteration, including the absence of angioedema as an indication for intubation. The study was approved by the institutional review boards of all participating centers. All data are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement (10).

### *Participant Selection*

All patients undergoing airway management for an indication of angioedema were eligible for analysis.

### *Data Source and Variables*

We collected data on patient demographics, characteristics, intubation outcomes, and disposition as well as methods of intubation including devices, sedation, paralysis, and adverse events. The primary outcome of interest was first-attempt intubation success. A detailed descrip-

tion of the NEAR network, and the methods of data collection, quality control, and data fields has been reported previously (6). We used published operational definitions in regard to attempts, methods, and intubation events (11). After each intubation, the intubating provider used a standardized electronic form to record data related to the patient, intubator, procedure, and immediate outcomes (StudyTRAX, Macon, GA). Study investigators reviewed all data using quality assurance algorithms to identify and correct data entry errors. Sites were required to ensure that 90% of all eligible patients were entered into NEAR. Enrolling centers that did not meet a minimum compliance rate of 90% were excluded from the analysis, as determined a priori.

### *Data Analysis*

We report data using descriptive statistics. We presented univariate descriptive data as proportions with cluster-adjusted 95% confidence intervals (CIs) and conducted all statistical analyses with SAS software (version 9.4; SAS Institute, Inc., Cary, NC).

## Results

### *Participants*

We identified complaint data on 19,071 discrete first-intubation encounters among 25 academic EDs during the study period. Of these, 4554 patients were excluded for an indication of “trauma” and 14,419 were excluded for a medical indication for intubation other than angioedema. The remaining 98 patients among 18 EDs who underwent an intubation attempt for angioedema, representing 0.5% (95% CI 0.3–0.7%) of all patients in the registry, comprised the study cohort.

### *Descriptive Data*

The median patient age was 59 years (interquartile range 42–64 years), and 27% (95% CI 16–37%) were female (Table 1). The youngest patient was 17 years old. Emergency physicians performed 94% (95% CI 86–100%) of first attempts. Emergency medicine senior residents (postgraduate year 3 and above) were the most common first attempt operators (58% [95% CI 37–79%]). An initial impression of difficult airway was recorded in 93% (95% CI 86–99%) of patients, and 78% (95% CI 67–84%) were deemed to have airway obstruction present. An orotracheal route was used during the first intubation attempt in 58% (95% CI 38–77%) of cases; the remaining 42% (95% CI 23–62%) were nasotracheal. Flexible endoscopes were the most commonly used initial devices (49% [95% CI 39–59%]), followed by the

**Table 1. First Attempt Intubation Characteristics and First-Pass Success**

Variable	Initial Attempt, n (% [95% CI])	First Attempt Successful, n	First Attempt Successful, % (95% CI)
All angioedema patients	98 (100)	79	81% (66–96%)
Sex (N = 98)			
Female	26 (27% [16–37])	23	88% (70–98%)
Male	72 (74% [63–84%])	56	78% (66–87%)
Habitus (N = 98)			
Very thin	2 (2% [0–5%])	1	50% (1–99%)
Thin	7 (7% [1–13%])	5	71% (29–96%)
Normal	39 (40% [28–52%])	33	85% (69–94%)
Obese	41 (42% [34–50%])	34	83% (68–93%)
Morbidly obese	9 (9% [3–16%])	6	67% (30–93%)
Difficult airway characteristics			
Initial impression suggests difficulty (N = 93)	86 (93% [86–99%])	68	79% (69–87%)
Mallampatti (N = 96)			
I	5 (5% [1–10%])	5	100% (48–100%)*
II	11 (12% [5–18%])	9	82% (48–98%)
III	13 (14% [6–21%])	12	92% (64–100%)
IV	42 (44% [34–54%])	31	74% (58–86%)
Not assessed	25 (26% [18–36%])	20	80% (59–93%)
Airway obstruction present (N = 95)	74 (78% [67–84%])	60	81% (70–89%)
Need for immediate intubation (N = 98)	24 (25% [14–35%])	18	75% (53–90%)
Operator characteristics (N = 98)			
EM PGY1	4 (4% [0–9%])	2	50% (7–93%)
EM PGY2	21 (21% [8–35%])	16	76% (53–92%)
EM PGY3	47 (48% [27–69%])	39	83% (69–92%)
EM PGY4	10 (10% [0–20%])	7	70% (35–93%)
EM attending	10 (10% [3–18%])	5	50% (19–81%)
ENT attending	5 (5% [0–12%])	4	80% (28–99%)
Anesthesia non-attending (any PGY)	1 (1% [0–3%])	1	100% (3–100%)*
Device (N = 98)			
Flexible endoscope	48 (49% [39–59%])	42	88% (75–95%)
DL Macintosh	7 (7% [0–15%])	4	57% (18–90%)
DL Miller	1 (1% [0–3%])	0	0% (0–98%)*
VL, hyperangulated geometry	19 (19% [7–31%])	12	63% (38–84%)
VL, other	1 (1% [0–3%])	1	100% (3–100%)*
VL, standard geometry	22 (22%, 9–34%])	20	91% (71–99%)
Medications (N = 98)			
Sedation and paralysis	60 (61% [39–84%])	49	82% (70–90%)
Sedation only	10 (10% [0–23%])	5	50% (19–81%)
Topical anesthesia only	13 (13% [2–24%])	13	100% (75–100%)*
Topical with sedation	13 (13% [8–19%])	11	85% (55–98%)
No medications	2 (2% [0–5%])	1	50% (1–99%)

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Table 1. (continued)

Variable	Initial Attempt, n (%) [95% CI]	First Attempt Successful, n	First Attempt Successful, % (95% CI)
Route (N = 97)			
Oral	56 (58% [38–77%])	39	70% (56–81%)
Nasal	41 (42% [23–62%])	39	95% (83–99%)
Medication and route combinations (N = 97)			
Oral sedation and paralysis	47 (48% [38–59%])	36	77% (62–88%)
Oral sedation only	5 (5% [2–12%])	1	20% (1–72%)
Oral topical only	2 (2% [0–7%])	2	100% (16–100%)*
Oral topical with sedation	2 (2% [0–7%])	0	0% (0–84%)*
Nasal sedation and paralysis	12 (12% [7–21%])	12	100% (74–100%)*
Nasal sedation only	5 (5% [2–12%])	4	80% (28–99%)
Nasal topical only	11 (11% [6–19%])	11	100% (72–100%)*
Nasal topical with sedation	11 (11% [6–19%])	11	100% (72–100%)*
Nasal no medications	2 (2% [0–7%])	1	50% (1–99%)
Disposition (N = 97)			
ICU	96 (99% [94–100%])	77	80% (71–88%)
Operating room	1 (1% [0–6%])	1	100% (3–100%)*
Final outcome (N = 98)			
Rate of rescue surgical airway	2 (2% [0–7%])	NA	NA
Overall success rate	97 (99% [94–100%])	NA	NA

CI = confidence interval; DL = direct laryngoscopy; EM = emergency medicine; ENT = otorhinolaryngology; ICU = intensive care unit; NA = not applicable; PGY = postgraduate year; VL = video laryngoscopy.

\* One-sided 97.5% CI.

standard geometry video laryngoscope (22% [95% CI 9–34%]), and hyperangulated video laryngoscope (19% [95% CI 7–31%]). A sedative-hypnotic agent was administered during first intubation attempt in 85% (95% CI 62–100%) of encounters, and a neuromuscular blocking agent was administered in 61% (95% CI 39–84%) of patients.

#### First-Attempt Success

First-attempt success among all patients with angioedema was 81% (95% CI 71–88%). Nasotracheal intubations were associated with a success of 95% (95% CI 84–99%) while orotracheal routes were associated with a success of 70% (95% CI 56–81%). Flexible endoscopic devices were successful in 42 of 48 attempts (88% [95% CI 75–95%]). Rigid video laryngoscopes were successful in 33 of 42 attempts (79% [95% CI 63–90%]) and direct laryngoscopes in 4 of 8 attempts (50% [95% CI 16–84%]). Success in paralyzed and nonparalyzed pa-

tients was 82% (95% CI 70–91%) and 79% (95% CI 63–90%), respectively. First-attempt success was 100% (1-sided, 97.5% CI 75–100%) in patients undergoing intubation using topical anesthesia (n = 13 [nasotracheal n = 11; orotracheal n = 2]), without sedative or paralytic medication.

#### Adverse Events

Among all patients, 17 (17% [95% CI 10–26%]) experienced  $\geq 1$  peri-intubation adverse event during the first intubation attempt. Hypotension and hypoxia were the most common adverse events, occurring in 13 patients (13% [95% CI 5–22%]) and 12 patients (12% [95% CI 4–21%]), respectively. Other adverse events observed were esophageal intubation with delayed recognition (n = 2; 2% [95% CI 0–5%]), epistaxis (n = 1; 1% [95% CI 0–4%]), and vomiting (n = 1; 1% [95% CI 0–4%]).

Among the 19 patients requiring >1 intubation attempt, 13 (68% [95% CI 43–87%]) underwent a sec-

ond attempt with the same device. Tracheal intubation was achieved on second attempt in 10 patients (53% [95% CI 29–76%]). There were 8 patients who required  $\geq 3$  attempts. When the initial attempt was unsuccessful, cricothyrotomy was performed in 2 of 19 patients (11% [95% CI 1–33%]). No patients underwent a primary cricothyrotomy on the first attempt. The ultimate success rate was 99%; 1 patient did not have a documented outcome of the subsequent airway attempts. There were no recorded airway-related deaths.

## Discussion

To our knowledge, this study represents the largest prospective multicenter cohort of patients undergoing emergent tracheal intubation for angioedema in the ED setting. Patients with angioedema represented only 0.5% of ED intubations during the study period, which is congruent with existing literature. Angioedema represents a small proportion, 1 in 1000, of all ED visits in the United States (1). Only a minority of these patients will require intubation—7% among a contemporary cohort of 450 ED visits for angioedema (9). Emergency physicians were the primary operators in 94% of cases, and residents in advanced stages of training (postgraduate years 3 or 4) most frequently performed the procedure (58%). While an uncommon occurrence, tracheal intubation in patients with angioedema can be particularly challenging because of anatomic distortion of the upper airway. Achieving intubation on the first attempt is important because of increasing peri-intubation adverse events with cumulative attempts (12–14). A wide array of devices and techniques were used in this cohort, likely representing the variability in the presentation of acute angioedema as well as variation in provider comfort with different airway management techniques. A recent observational study analyzing video footage of 45 patients undergoing tracheal intubation for angioedema at 1 academic medical center reported similar findings: emergency physicians used a broad range of methods to manage these patients (8).

Success was achieved on the initial attempt in 81% of patients with angioedema. We observed an unexpectedly high success rate of 88% among patients undergoing flexible endoscopic intubation techniques. In addition, nasotracheal first attempts were observed to have higher success than orotracheal routes (95% vs. 70%, respectively). These observations are discrepant from a report from the NEAR III investigators, who reported that flexible endoscopic intubation in the ED setting between 2002–2012, for any indication, was associated with 51% first-attempt success (5). While our findings offer compelling evidence that flexible endoscopic techniques are used with favorable outcomes in patients with angioedema, these results

should be interpreted with caution for several reasons. Foremost, patients with angioedema selected for flexible endoscopic or nasal intubation may represent a dissimilar group, possibly of greater clinical stability, than those selected for rapid sequence intubation (RSI) or oral attempts. An example comparison would be a patient with severe tongue and soft palate angioedema requiring intubation who is presently maintaining airway patency and able to tolerate awake attempts vs. a stridulous patient presenting in extremis who is unable to tolerate awake intubation. The former patient is likely suitable for an awake, flexible endoscopic approach, while the latter might be managed with a “forced to act” or “one best attempt” RSI approach, followed by a cricothyrotomy if unsuccessful. Furthermore, there is no standard definition for what represents an “attempt” with an endoscopic device. More than 1 attempt to intubate the trachea may occur without requiring the operator to fully withdraw the endoscope, falsely inflating success and inaccurately reflecting the complex nature of navigating a flexible endoscope in this population. It is important to note that given our small sample size we are unable to demonstrate superiority of a given technique. However, our findings suggest that flexible endoscopic and nasotracheal approaches, in appropriately selected patients, are feasible and associated with desirable outcomes in the ED setting.

Choosing intubation techniques with the highest probability of success is essential because multiple intubation attempts are associated with peri-intubation complications (12,13). Difficult intubation is expected to occur with greater frequency in this population given the inherent anatomic distortion among patients with angioedema. While a difficult airway was suspected in 93% of patients, only 78% had documented obstruction. This may imply that  $\leq 22\%$  of patients were intubated for their anticipated clinical course or possibly for interfacility transfer. No patients underwent a primary cricothyrotomy, though 11% of those with a failed first attempt required a surgical airway to achieve tracheal intubation. One patient in the cohort experienced failure of the first and second attempts, with no additional data describing subsequent attempts, though death was not reported. It is possible, though not certain, that attempts were aborted in this case in favor of continued observation. Thus, we report an ultimate tracheal intubation success rate of 99%, with no patient deaths.

Consensus statements, based largely on expert recommendations, advise against RSI when angioedema is so severe that the upper airway cannot be directly visualized (15). We observed that the combination of an induction agent and paralytic agent were administered in 61% of attempts, with success in 82%. The prevalence of RSI observed may be related to several factors. Foremost, emergency physicians are highly comfortable with RSI

as a primary method and are highly proficient in its use. Given this, providers less comfortable with awake or flexible endoscopic techniques may choose a familiar method when faced with an anatomically difficult airway. Second, providers may underestimate the difficulty of oral laryngoscopy in the patient with severe airway edema. Lastly, some patients who are intubated for their anticipated clinical course may have less severe angioedema at the time of intubation, rendering an orotracheal RSI attempt feasible. Our data suggest that RSI may be a reasonable approach for appropriately selected patients intubated for angioedema and may be preferable for some providers given their comfort and skill level with this approach relative to flexible endoscopic techniques.

We observed success among those undergoing awake techniques to be higher than those in whom a sedative medication with or without a paralytic agent was used. Success with topical anesthesia alone, without sedative administration, was 100%. Among those undergoing awake techniques, 11 of 13 patients underwent a nasal approach. This may confound interpretation of “first-attempt success” given the lack of consensus definition of an attempt, as discussed above. In addition, the population who underwent RSI may include patients who were severely obstructed upon presentation or presented in extremis, representing a “forced to act” scenario for providers. Patients in whom obstruction has progressed to near asphyxiation are unsuitable for an awake endoscopic approach, given the time and patient compliance required for the procedure to be performed. The decision to perform RSI should be made with appropriate caution, only after careful examination of the patient’s presenting condition and development of a clearly defined rescue plan, including cricothyrotomy. Awake intubation, ideally using indirect techniques and topical anesthetic agents, should be strongly considered when a difficult airway is anticipated and the patient is presently maintaining airway patency and is not in extremis.

### Limitations

Our study has several limitations. Angioedema is an uncommon presenting complaint, and the frequency with which angioedema patients require intubation in the ED is low. The small cohort size limited our statistical analysis to descriptive techniques, and our data should not be misconstrued as to indicate that one technique is superior to another. In addition, we focused primarily on the first attempt at intubation because failure of the first attempt is associated with adverse outcomes. Further, we were unable to determine the frequency of “forced to act” scenarios with critical airway obstruction vs. anticipatory intubations in the setting of concern for angioedema progression. This may explain why we observed a higher than

expected rate of RSI in this cohort. Of note, 12 patients were reported to undergo intubation via a nasal route with concurrent administration of a paralytic. This would be a highly atypical practice, excepting in cases where a rigid, orally inserted laryngoscope was used with forceps to guide a nasally inserted tracheal tube (2% in this cohort), and may represent erroneous recording of a paralytic medication administered after the intubation. As our study is based upon a retrospective analysis of a prospectively collected observational data, we are unable to further define what occurred in this small subset of patients. In addition, although this is a prospective registry study, and data are expected to be entered in real time, recall bias and recall errors may have occurred. Providers entering registry data have many options to consider when choosing intubation indication, including “angioedema,” “anaphylaxis,” and “airway obstruction (not angioedema/anaphylaxis).” It is possible that some patients intubated for angioedema were not captured because of misclassification. Finally, selection bias may arise secondary to the composition of NEAR, whom some may suggest comprises institutions with a more prominent focus on emergency airway management or higher than average access to advanced airway equipment.

### Conclusions

In this retrospective review of a multicenter, prospectively collected cohort of patients with angioedema undergoing tracheal intubation in the ED, we observed first-attempt success in 81% using a range of devices and techniques, including flexible endoscopic and video laryngoscopy. RSI was the most common method used (61%), though we observed that other intubation techniques, such as awake intubation, were also used with frequency and with high efficacy.

### Acknowledgments

Presented at the American College of Emergency Physicians Scientific Assembly, October 28, 2019, Denver, CO. BJS, RLC, and CAB conceived the study. BJS, XL, RLC, and AHK designed the trial. CAB supervised the conduct of the trial and data collection. BJS and AHK managed the data, including quality control. BED, RMW, JNC, and RLC provided statistical advice on study design. AHK and BJS analyzed the data. BJS, XL, RLC, and CAB drafted the manuscript. All authors contributed substantially to the manuscript revision. BJS takes responsibility for the article as a whole.

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## ARTICLE SUMMARY

### 1. Why is this topic important?

Patients with angioedema may present with life-threatening airway involvement, the need for emergent intubation, and a difficult airway. Little is known about our current emergent airway management practices in this population.

### 2. What does this study attempt to show?

We sought to describe contemporary airway management practices, patient characteristics, and outcomes among patients undergoing endotracheal intubation in the emergency department for angioedema.

### 3. What are the key findings?

We found that intubation for angioedema was an uncommon indication for intubation in this large, multicenter cohort (0.5%). Emergency physicians managed the airway in 94% of encounters, and most patients were deemed to have a difficult airway (93%). Diverse devices, including flexible endoscopes and rigid video laryngoscopes, and pharmacologic methods, ranging from topical-only to rapid sequence intubation, were used to manage the airway with an overall first-attempt success rate of 81%.

### 4. How is patient care impacted?

While uncommon, the patient with angioedema requiring intubation almost universally presents with a difficult airway. In this cohort, we found that numerous advanced airway techniques were used by emergency physicians. Maintenance of competence in a diverse array of advanced airway procedural techniques is imperative for caring for this patient population.