Supplementary Appendix:

Study Protocol and Statistical Analysis Plan

Title:	Bougie or Stylet In Patients Undergoing Intubation Emergently (BOUGIE) trial
Manuscript:	Bougie versus Stylet for Tracheal Intubation of Critically Ill Adults ClinicalTrials.gov number, NCT03928925
Authors:	Brian E. Driver, Matthew W. Semler, Wesley H. Self, Adit A. Ginde, Stacy A. Trent, Sheetal Gandotra, Lane M. Smith, David B. Page, Derek J. Vonderhaar, Jason R. West, Aaron M. Joffe, Steven H. Mitchell, Kevin C. Doerschug, Christopher G Hughes, Kevin High, Janna S. Landsperger, Karen E. Jackson, Michelle P. Howell, Sarah W. Robison, John P. Gaillard, Micah R. Whitson, Christopher M. Barnes, Andrew J. Latimer, Vikas S. Koppurapu, Bret D. Alvis, Derek W. Russell, Kevin W. Gibbs, Li Wang, Christopher J. Lindsell, David R. Janz, Todd W. Rice, Matthew E. Prekker, Jonathan D. Casey, for the BOUGIE Investigators and the Pragmatic Critical Care Research Group.

This Supplementary Appendix contains the following items:

1) Original Study Protocol [dated 19 April 2019]

2) Final Study Protocol [16 January 2020]

3) Summary of changes to Study Protocol

4) Original Statistical Analysis Plan [dated 8 December 2020]

5) Final Statistical Analysis Plan published online [dated 25 May 2021]

6) Summary of changes to Statistical Analysis Plan

Clinical Trial Protocol

Study Title	Bougie or Stylet In Patients Undergoing Intubation Emergently (BOUGIE): a randomized, multi-center trial
Acronym	BOUGIE
Version	Version 1.0
Date	April 19, 2019
Protocol Co-Chairs	Brian Driver MD Assistant Professor of Emergency Medicine Hennepin County Medical Center and University of Minnesota Matthew Prekker MD, MPH Assistant Professor of Emergency Medicine and Pulmonary and Critical Care Medicine Hennepin County Medical Center and University of Minnesota
Coordinating Center	Vanderbilt University Medical Center Director: Jonathan D. Casey MD ED Site Director: Wesley H. Self, MD, MPH ICU Site Director: Todd W. Rice, MD, MSc
Network	Pragmatic Critical Care Research Group (PCCRG) Steering Committee Chair: Matthew W. Semler MD, MSc

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Trial Summary

Title: Bougie or stylet in patients undergoing intubation emergently (BOUGIE) trial. A randomized trial of bougie use on the first intubation attempt to improve the safety and efficiency of tracheal intubation among critically ill adults.

Background: Complications are common during tracheal intubations performed outside of the operating room. Successful intubation on the first attempt has been associated with a lower rate of procedural complications, but the proportion of critically ill patients intubated on the first attempt during tracheal intubations outside of the operating room is less than 90%. The bougie, a thin semi-rigid tube that can be placed into the trachea, allowing a Seldinger-like technique of intubating a patient's airway, has been traditionally reserved for difficult or failed airways. However, a recent single center trial of adult patients intubated in an emergency department demonstrated that use of the bougie on the first attempt improved intubation success, compared to use of a traditional stylet. We propose a multi-center randomized trial to compare first-attempt bougie use versus endotracheal tube with stylet use for tracheal intubation of critically ill adults in the ED and ICU.

Primary aim: To compare the effect of bougie use versus endotracheal tube with stylet use on the incidence of successful intubation on the first attempt among adults undergoing urgent or emergent tracheal intubation.

Secondary aim: To compare the effect of bougie use versus endotracheal tube with stylet use on the incidence of severe hypoxemia among adults undergoing urgent or emergent orotracheal intubation.

Primary hypothesis: Bougie use will increase the incidence of successful intubation on the first attempt among adults undergoing urgent or emergent intubation

Secondary hypothesis: Bougie use will decrease the incidence of severe hypoxemia among adults undergoing urgent or emergent intubation

Inclusion criteria:

1. Patient is at least 18 years old
2. Patient is located in a participating unit
3. Planned procedure is tracheal intubation with sedative administration (or tracheal intubation without sedative administration during cardiac arrest)
4. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit
5. Planned laryngoscopy device is a non-hyperangulated laryngoscope blade

Exclusion criteria:

1. Patient is pregnant
2. Patient is a prisoner
3. Urgency of intubation precludes safe performance of study procedures

4. Operator feels an approach to intubation other than use of a bougie or use of an endotracheal tube with stylet would be best for the care of the patient
5. Operator feels use of a bougie is required or contraindicated for the care of the patient
6. Operator feels use of an endotracheal tube with stylet is required or contraindicated for the care of the patient

Consent: Given that use of a bougie and use of an endotracheal tube with stylet are both routine approaches during the first attempt at tracheal intubation in the ED and ICU; the lack of established risk or benefit with either approach; and the impracticability of obtaining informed consent prior to urgent or emergent tracheal intubation among critically ill patients, a waiver of informed consent will be requested.

Randomization: Using opaque envelopes available in participating units, participants will be randomized 1:1 to use of a bougie versus use of an endotracheal tube with stylet on the first intubation attempt.

Study interventions:
1. Bougie: a straight, semi-rigid, disposable bougie > 60 cm in length will be used to intubate the trachea during laryngoscopy, then an assistant will load an appropriately-sized endotracheal tube over the bougie and the operator will advance the tube over the bougie into the trachea.
2. Endotracheal tube with stylet: an endotracheal tube with pre-loaded malleable stylet will be used to intubate the trachea during laryngoscopy.

Primary outcome:
Successful intubation on the first attempt

Secondary outcome:
Incidence of severe hypoxemia (lowest arterial oxygen saturation between induction and two minutes following intubation of less than 80%). Induction is defined as when the sedative agent is administered.

Exploratory outcomes:
- Cormack-Lehane grade of glottic view
- Number of laryngoscopy attempts
- Number of attempts at passing bougie
- Number of attempts at passing endotracheal tube
- Time from induction to intubation
- Operator-assessed difficulty of intubation
- Incidence of mechanical intubation complications, including:
    - Esophageal intubation
    - Airway injury
    - Aspiration noted during the intubation attempt
- Incidence of peri-intubation cardiovascular collapse defined as any of:
    - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation

    - New or increased vasopressor between induction and 2 minutes following intubation
    - Cardiac arrest within 1 hour of intubation
    - Death within 1 hour of intubation
- Cardiac arrest within 1 hour of intubation
- ICU-free days in the first 28 days
- Ventilator free days in the first 28 days
- 28-day all-cause in-hospital mortality

1 Background

Tracheal intubation of critically-ill adults is frequently performed in the Emergency Department (ED) and Intensive Care Unit (ICU). Successful intubation on the first attempt has been associated with reduced peri-intubation complications.[1] However, less than 90% of patients are intubated on the first attempt in most settings outside of the operating room, highlighting an opportunity for improvement.[2,3]

Tracheal intubation involves the administration of procedural medications (induction), use of a direct or video laryngoscope to obtain a view of the glottic structures (laryngoscopy), and passage of an endotracheal tube through the vocal cords (intubation). The final step of the procedure, intubation, may be performed by passing a bougie (a disposable tracheal tube introducer of approximately 70 cm in length) through the vocal cords and then passing an endotracheal tube over the bougie and into the trachea, or by directly placing an endotracheal tube (preloaded with a malleable stylet) into the trachea. It is unknown whether using a bougie or an endotracheal tube with stylet is more likely to result in successful placement of an endotracheal tube in the trachea on the first attempt at laryngoscopy and intubation. Some providers routinely use a bougie on the first attempt, with studies reporting the use of a bougie during the first intubation attempt in up to 80% of procedures.[4] Other providers most commonly use an endotracheal tube with stylet on the first attempt, reserving the bougie as a backup device in cases of suboptimal laryngoscopic view, with other studies reporting the use of a bougie in less than 5% of intubation attempts.[2]

Only one prior randomized trial has compared use of a bougie versus endotracheal tube with stylet for tracheal intubation outside of the operating room. This single-center trial found a significantly higher rate of first attempt intubation success with bougie use (98%) compared to the endotracheal tube with stylet (87%) in adult patients undergoing emergent tracheal intubation in the ED.[5] There were no differences between the two groups in rates of complications or clinical outcomes. Operators in this single-center trial had substantial familiarity with the bougie. This device was used on the first intubation attempt in approximately 80% of procedures before the trial began.[4] It is unknown if these results will generalize to other settings where operators use the bougie less frequently than the may have less experience with the use of a bougie and more experience with using an endotracheal tube with stylet.

2 Rationale, Aims, and Hypotheses

To determine if the use of a bougie increases the incidence of successful intubation on the first attempt in a broad variety of practice settings among a population of operators with varied prior experience with bougie and endotracheal tube with stylet, a multi-center randomized trial is needed.

2.1 Study Aims

- Primary:

- To compare the effect of bougie use versus endotracheal tube with stylet use on successful intubation on the first attempt among adults undergoing urgent or emergent tracheal intubation

- Secondary:
  To compare the effect of bougie use versus endotracheal tube with stylet use on the incidence of severe hypoxemia (lowest arterial oxygen saturation between induction and two minutes following intubation of less than 80%). Induction is defined as when the sedative agent is administered.

2.2 Study Hypotheses

- Primary:
  - Bougie use will increase the incidence of successful intubation on the first attempt among adults undergoing urgent or emergent intubation

- Secondary
  - Bougie use will decrease the incidence of severe hypoxemia among adults undergoing urgent or emergent intubation

3 Study Description

To address these aims, we propose a multi-center, non-blinded, parallel-group, randomized clinical trial evaluating the effect of using a bougie versus using an endotracheal tube with stylet on successful intubation on the first attempt. Patients located in participating EDs and ICUs who are deemed by the treating physicians to require tracheal intubation and who are appropriate according to inclusion/exclusion criteria will be enrolled and randomly assigned to bougie use versus endotracheal tube with stylet use on the first intubation attempt. All other decisions regarding airway management will remain at the discretion of the treating physician. Data will be prospectively collected at the time of intubation by an independent observer and supplemented with review of the medical record to determine the effect of the assigned interventions on study outcomes.

4 Study Population, Inclusion and Exclusion Criteria

4.1 Study Population

The study population will be critically-ill adults for whom the clinical team has elected to perform tracheal intubation via the oral route using a non-hyperangulated blade (Macintosh or Miller-style). To be eligible for enrollment, the patient must meet all inclusion criteria and none of the exclusion criteria.

4.2 Inclusion Criteria

1. Patient is at least 18 years old
2. Patient is located in a participating unit
3. Planned procedure is tracheal intubation with sedative administration (or tracheal intubation without sedative administration during cardiac arrest)
4. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit
5. Planned laryngoscopy device is a non-hyperangulated laryngoscope blade

Examples of qualifying laryngoscope blades include: traditional Miller blade and handle; traditional Macintosh laryngoscope blade and handle; Medtronic McGrath™ MAC Video Laryngoscope; KARL STORZ C-MAC® Video Laryngoscope; GlideScope MAC S3 & S4 blades or T3/4

Examples of non-qualifying laryngoscope blades include: GlideScope Ranger; GlideScope AVL™; KARL STORZ C-MAC D-Blade

4.3 Exclusion Criteria

Exclusion criteria:

1. Patient is pregnant
2. Patient is a prisoner
3. Urgency of intubation precludes safe performance of study procedures
4. Operator feels an approach to intubation other than use of a bougie or use of an endotracheal tube with stylet would be best for the care of the patient
5. Operator feels use of a bougie is required or contraindicated for the care of the patient
6. Operator feels use of an endotracheal tube with stylet is required or contraindicated for the care of the patient

5 Enrollment and Randomization

5.1 Study Sites:

1. Vanderbilt University Medical Center Medical Intensive Care Unit
2. Vanderbilt University Medical Center Emergency Department

5.2 Enrollment

All patients will be enrolled at the time the clinical team elects to intubate and the patient meets all inclusion criteria but no exclusion criteria. Patients who are enrolled but have a change in clinical status precluding intubation (e.g. resolution of respiratory failure or death prior to procedure) will be prospectively recorded.

5.3 Consent

Intubation using a bougie and intubation using an endotracheal tube with stylet are both accepted practice in urgent or emergent intubation in adults. Currently, there are no evidence-based guidelines to inform practice in this area, and there is significant variation in practice between providers.

Patients requiring intubation in the ED or ICU are critically ill and are at significant risk for morbidity and mortality as a result of their underlying illness. Moreover, each patient undergoing intubation in routine clinical care receives intubation using either a bougie or an endotracheal tube with stylet on the first attempt. Thus, the benefits or risks of these two approaches are experienced by patients undergoing intubation in clinical care, outside the context of research. For every patient enrolled in the proposed trial, the treating clinicians specifically feels that either a bougie or an endotracheal tube with stylet would be a safe approach for the patient (otherwise the patient is excluded). Therefore, making the decision between the two approaches randomly (by study group assignment) rather than by a provider who thinks either approach is safe for the patient, is felt by the investigators to pose minimal additional risk.

In summary, because both approaches to tracheal intubation being studied are (1) commonly used as a part of routine care, (2) are interventions to which the patient would likely be exposed even if not participating in the study, and (3) are acceptable options from the perspective of the treating clinicians (otherwise the patient is excluded), and (4) there are no established risk or benefit with either approach, we feel the study meets criteria for minimal risk.

Additionally, obtaining informed consent in the study would be impracticable. Tracheal intubation of acutely ill patients is a time-sensitive procedure. Despite the availability of a formal informed consent document for the procedure itself, time allows discussion of risks and benefits in less than 10% of airway management events in the study settings.

Because the study poses minimal risk, would not adversely affect the welfare or privacy rights of the participant, and consent would be impracticable, we will request a waiver of informed consent.

Previous randomized trials comparing two standards of care for emergency intubation have been completed under a waiver of informed consent.[5–12]

Information regarding the study will be made available to patients and families by one of three mechanisms: (1) a patient and family notification sheet provided to each patient and family following enrollment informing the patient of his or her enrollment and describing the study, (2) a patient and family information sheet posted in at least three publicly-visible locations within the study unit containing general information about the study and contact information for the research team for additional questions or concerns, (3) a patient and family information sheet provided to each patient and family on admission as part of an "admission packet" containing general study information and contact information for the research team for additional questions or concerns. Which mechanism of providing information to patients and families will be used at each study site will be determined by site investigators in coordination with the local context assessment of the site IRB.

5.4 Randomization

After enrollment, patients will be randomized in a 1:1 ratio to undergo intubation using a bougie or using an endotracheal tube with stylet for the first attempt. The randomization will be performed using permuted blocks of two, four, and six. The randomization will be stratified by study site (each participating ED and ICU is a different stratum). The study assignments will be placed in opaque randomization envelopes and will be available to operators in participating units. Study group assignment will remain concealed to study personnel and operators until after the decision has been made to enroll the patient in the study and the operator has declared their choice of laryngoscope.

6 Study Procedures

6.1 Study Interventions

The study group assignment will determine only the first device that the operator will attempt to use to intubate the trachea (bougie or endotracheal tube with stylet).

Prior to opening the randomization envelope and revealing the study assignment, the operator will select a laryngoscope with a non-hyperangulated curved blade and will indicate their selection by circling the name of the laryngoscope on the front of the randomization envelope.

After selecting a laryngoscopy device, and receiving study group assignment, the operator will proceed with the procedure. All other aspects of the intubation procedure will be at the discretion of the operator, including endotracheal tube diameter, patient position, pre-oxygenation, approach to ventilation and oxygenation during intubation, and any devices used following the first intubation attempt. Use of video assistance during direct laryngoscopy, if available, is a dynamic decision during the procedure and will be at the discretion of the operator for any selected device capable of video assistance.

Although the study assignment stipulates the first device for intubating the trachea, if there are difficulties with intubation the operator is free to use any other method of intubation, including crossover to the other treatment group. Tracheal intubation will be confirmed with capnography.

6.1.1 Bougie Group

This trial seeks to evaluate the use of straight, semi-rigid bougies because they are likely to be more effective than less-rigid bougies packaged in a curled position. The latter type of bougie may be more difficult to advance through the glottic opening.[13] The BEAM trial found an absolute between-group difference of 11% for first attempt success, favoring the group intubated with a 70 cm, semi-rigid, malleable, straight bougie with a coude tip (SunMed). Therefore, participating units will use a straight bougie at least 60 cm in length; a coude tip is favored but not required. Operators may choose whether and how to bend the bougie prior to intubation.

In the bougie group, the operator will attempt to pass the bougie into the trachea. If successful, an assistant will load the endotracheal tube (no stylet) over the bougie and the operator, without removing the laryngoscope from the mouth, will guide the tube through the vocal cords to the desired depth in the trachea. If resistance is encountered when passing the endotracheal tube over the bougie (presumably from the bevel-tip of the tube catching on the arytenoid cartilages), the tube will be retracted 2 centimeters, rotated 90° counterclockwise, and readvanced into the trachea. It is acceptable but not encouraged to pre-load the endotracheal tube onto the bougie before intubating the trachea. An assistant will remove the bougie from within the endotracheal tube prior to manual ventilation and capnographic confirmation. During bougie removal, the operator must hold the tube firmly in the desired tracheal position to avoid inadvertent tracheal extubation. If the bougie is not successfully placed in the trachea or the endotracheal tube successfully advanced over the bougie on the first attempt at intubation, the operator may use any approach to additional attempts at tracheal intubation.

6.1.2 Endotracheal tube with stylet use

In the endotracheal tube with stylet group, the operator will attempt to intubate the trachea with an endotracheal tube containing a removeable, malleable stylet. Manipulation of the shape/curve of the endotracheal tube with stylet is at the discretion of the operator before the first intubation attempt, however a "straight-to-cuff" shape and a bend angle of 25° to 35° is encouraged. If difficulty in passage is encountered, the operator can withdraw, rotate, or reshape the tube and stylet as needed. The stylet will be left in place until the tube is advanced to the trachea.

6.1.3 Operator training

An online training video summarizing best practices in use of both the bougie and endotracheal tube with stylet will be made available to all operators at participating units. Before trial enrollment begins, operators routinely expected to perform tracheal intubation in each unit will attest to viewing the online training video. In addition, the randomization sheet will contain reminders of best-practices for each group.

The randomization sheet for the bougie group will suggest that:

1. Following placement of the bougie in the trachea, an assistant should load the endotracheal tube (no stylet) over the bougie
2. The laryngoscope should remain in place while the operator advances the endotracheal tube over the bougie, rotating the tube 90° counterclockwise as it passes the vocal cords

The randomization sheet for the endotracheal tube with stylet group will suggest that:

1. A "straight-to-cuff" shape and a bend angle of 25° to 35° is encouraged (with a stock photo demonstrating the suggested shape).
2. If intubation is difficult or unsuccessful, the operator can withdraw, reshape, or rotate the tube as needed

7 Data Collection and Outcome Measures

7.1 Data Collection

All data are collected non-invasively as a part of current usual care. No additional data will be obtained beyond that which is obtained by bedside observation and from the electronic medical record.

Important peri-procedural outcomes will be captured by an independent, in-person observer not participating in the tracheal intubation procedure. These independent observers will be trained and use standardized data collection forms. They will be responsible for capturing the primary endpoint for this trial, successful intubation on the first attempt. To ensure a standardized application of the endpoint definition, an online instructional video will be created explaining how to record the number of attempts. The video will demonstrate the scoring process in several example intubation procedures, performed by the principal investigators using both the bougie and the endotracheal tube with stylet. This video will be available to all independent observers throughout the procedure.

The following variables will be recorded:

Baseline: Age, gender, height, weight, body mass index, race, APACHE II score, active medical problems at the time of intubation, active comorbidities complicating intubation, vasopressor use prior to intubation, noninvasive ventilator use, high flow nasal cannula use, highest FiO_2 delivered in prior 6 hours, indication for intubation, reintubation within 72 hours of extubation, preoxygenation technique, and operator experience.

Peri-procedural: Date and time of sedative administration, oxygen saturation and systolic blood pressure at time of sedative administration, lowest arterial oxygen saturation from induction to two minutes after intubation, lowest and highest systolic blood pressure from induction to two minutes after intubation, vasopressor administration, time from induction to intubation, number of times a laryngoscope entered the mouth, number of times a bougie entered the mouth, and number of times an endotracheal tube entered the mouth will be collected by a trained, independent observer not affiliated with the performance of the procedure. Sedative agent name and dose, neuromuscular blocking agent name and dose, use of bag-valve-mask ventilation, laryngoscope type, best Cormack-Lehane glottic view on the first attempt, percent of glottic opening, viewing the screen of a videolaryngoscope during the first attempt, total number of attempts, presence of aspiration between induction and intubation, rescue device use, need for additional operators, presence of predictors of difficult laryngoscopy (body fluids obscuring glottic view, cervical immobilization, facial trauma, airway obstruction or edema), and mechanical complications (esophageal intubation, airway trauma) will be obtained from the operator. Additional outcomes of the airway procedure will be obtained from retrospective chart review.

0-24 hours: Post-intubation shock or cardiac arrest, post-intubation pneumothorax, oxygen saturation, FiO_2, PEEP, and mean arterial pressure at 24 hours after intubation.

In-Hospital Outcomes: Ventilator-free days, ICU-free days, date of death

7.2 Outcome Measures

7.2.1 Primary Outcome

The primary outcome is successful intubation on the first attempt. Successful intubation on the first attempt is defined as placement of an endotracheal tube in the trachea (confirmed by standard means including capnography) following: (1) a single insertion of a laryngoscope blade into the mouth and (2) EITHER a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube into the mouth OR a single insertion of an endotracheal tube with stylet into the mouth.

7.2.2 Secondary Outcome

The secondary trial outcome is the incidence of severe hypoxemia. Severe hypoxemia is defined as an oxygen saturation less than 80% during the time interval from induction to two minutes after completion of the intubation procedure.

7.2.3 Exploratory Outcomes

- Cormack-Lehane grade of glottic view
- Number of laryngoscopy attempts
- Number of attempts at passing bougie
- Number of attempts at passing endotracheal tube
- Time from induction to intubation
- Operator-assessed difficulty of intubation
- Whether the video laryngoscope screen was viewed
- Incidence of mechanical intubation complications, including:
    - Esophageal intubation
    - Aspiration noted during the intubation attempt
    - Airway trauma
- Cardiac arrest within 1 hour following intubation
- Incidence of peri-intubation cardiovascular collapse defined as any of:
    - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation
    - New or increased vasopressor between induction and 2 minutes following intubation
    - Cardiac arrest within 1 hour following intubation
    - Death within 1 hour following intubation
- ICU-free days in the first 28 days
- Ventilator free days in the first 28 days
- 28-day all-cause in-hospital mortality

8 Risks and Benefits

Both bougie use and endotracheal tube with stylet use are both accepted standards of care. Both approaches to intubation are routinely used in the study units. There are no known risk differences between the two intubation modalities. In the only randomized trial comparing these intubation strategies, there were no differences in clinical outcomes or complications. For this reason, there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by critically ill patients requiring tracheal intubation as part of routine care. The societal benefit of this study could be substantial in the form of improved understanding of safe and effective airway management outside of the operating room.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. REDCap tools will be used to ensure that the PHI that is collected is only visible to investigators at the healthcare system where the patient as enrolled. To protect participant privacy, REDCap tools will be used to ensure that only deidentified data can be exported for use during analysis.

9 Safety Monitoring and Adverse Events

9.1 Safety Monitoring

The study will take place in EDs and ICUs at the time of a procedure required for routine clinical care. Thus, at the time of study intervention, the patient will have in the room: a physician trained in the care of critically ill adults, a critical care or emergency medicine nurse, and usually a respiratory therapist. The patient will be receiving continuous invasive or non-invasive monitoring. Any and all complications, whether or not related to the study, will be cared for in real-time by these physicians. Additionally, if at any point the treating team believes it is unsafe to use either the bougie or endotracheal tube with stylet, the study intervention will be halted and the patient will be intubated in the manner deemed safest by the treating team.

A Data and Safety Monitoring Board (DSMB) will oversee the trial. Interim analyses for safety and efficacy will be conducted as described in the Statistical Analysis section of the protocol.

10.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation participant administered an intervention that does not necessarily have to have a causal relationship with this treatment. An adverse event therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an intervention, whether or not the incident is considered related to the intervention.

A serious adverse event (SAE) is defined as any unexpected and untoward medical occurrence that meets any of the following criteria:

1. Results in death
2. Is life threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
3. Requires inpatient hospitalization
4. Prolongs an existing hospitalization
5. Results in persistent or significant disability or incapacity
6. Results in a congenital anomaly or birth defect
7. Important medical event that requires an intervention to prevent any of 1-6 above.

The overall principal investigator and site principal investigators will be responsible for overseeing the safety of this trial on a daily basis. They will be available any time for questions from the clinical team, who will also be monitoring the patients continuously for adverse events and serious adverse events. Serious and unexpected adverse events potentially associated with study interventions will be recorded in a case report form in the study record and promptly reported to the IRB. As tracheal intubation in the critical care setting is known to be independently associated with numerous adverse events including failed attempts at intubation, esophageal intubation, arterial oxygen desaturation, aspiration, hypotension, cardiac arrest, and death, these events will be continuously monitored by study personnel to determine if a preponderance of adverse events in one study group merits stoppage of the trial. However, in the absence of an imbalance of the above events between study groups, these events are expected in the routine performance of the airway management procedure and will not be individually recorded and reported to the IRB as unexpected adverse events.

Communication and Reporting of Adverse Events. In order to ensure proper and timely reporting of all adverse events, there will be a clear communication plan for all study personnel to follow. Serious and unexpected adverse events potentially associated with study interventions will be reported to the PI within 72 hours of occurrence and recorded in a case report form in the study record. The PI will, in turn, report all SAEs potentially related to study procedures to the IRB and DSMB within 7 calendar days of occurrence in accordance with IRB policy

As an additional safety measure, the exclusion criteria specifically state that airway management events in which the operator foresees the potential need for a specific intubation device (bougie, endotracheal tube with stylet, or other) will not be included in the trial so all airway management events studied will be those in which the treating clinical felt equipoise between the interventions being examined. Further, only the initial intubating device is proscribed by the study protocol and if at any time during the procedure the operator chooses to employ an alternative airway management strategy they are free to do so.

In addition, a DSMB containing at least one clinical investigator experienced in monitoring and conducting clinical trials in critically ill patients will oversee the study. In addition to assisting the PI with monitoring the trial for safety, the DSMB will also perform the interim analyses described in the statistical methods. If the data meet the stopping rules for efficacy at the interim analysis, the DSMB will communicate a recommendation to stop the trial at that time. In

addition, the DSMB will also be available to review unexpected serious adverse events in a timely manner. They will be asked to be available for rapid access by the investigators in the case of the need to evaluate unexpected serious adverse events or any other major unanticipated or safety related issues. Furthermore, in cases of unexpected serious adverse events, the DSMB will have the ability to pause the trial to investigate possible safety issues and/or suggest changes to the design of the study to abrogate any safety issues.

10.3 Study Withdrawal

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI.

The reason and date of every withdrawal will be recorded in the patient study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or other safety parameter that could have led to discontinuation. Follow-up will be conducted until the condition has resolved, until diagnosis of the adverse event or safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well.

11 Statistical Considerations

11.1 General Considerations

We will present summary tabulations by treatment group. For categorical variables, the number and percentage of patients within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of patients, mean or median as appropriate, and standard deviation or interquartile range as appropriate, will be presented.

Formal statistical hypothesis testing will be performed on the primary and secondary outcomes, with all tests conducted at the 2-sided, 0.05 level of significance.

11.2 Sample Size Estimation

A prior single-center randomized trial reported an absolute difference of 11% in successful intubation on the first attempt between the bougie and endotracheal tube with stylet groups. Because this trial occurred in an ED that was already familiar with bougie use, the difference in successful intubation on the first attempt that could be achieved in other settings may be of lesser magnitude. Additionally, successful intubation on the first attempt in intensive care units has traditionally been lower than in ED settings.[2,3,10,11] Therefore, the current trial will be designed to detect a 6% absolute difference between groups in the incidence of successful intubation on the first attempt. Assuming an incidence of successful intubation on the first laryngoscopy

attempt of 84% in the endotracheal tube with stylet group, detecting a 6% absolute increase in the incidence of successful intubation on the first attempt with 80% power at a two-sided alpha level of 0.05 would require enrollment of 1,050 patients (525 per group). Anticipating missing data for 5% of patients or less, we will plan to enroll a total of 1,106 patients (553 per group).

This sample size calculation was performed in STATA version 15.1 with the following command: sampsi 0.90 0.84, p(0.8).

11.3 Analysis Populations

The intent-to-treat (ITT) population will be the primary outcome analysis population. Patients who meet any exclusion criterion will not be a part of the ITT population and will be considered screening failures.

11.4 Statistical Analysis

Prior to the conclusion of enrollment, we will make publicly available a complete final statistical analysis plan. Analyses conducted in accordance with the statistical analysis plan will be identified as *a priori*. Any additional analyses requested by the investigators or reviewers will be identified as *post hoc*.

11.4.1 Primary Analysis

Unadjusted test of treatment effect. The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to the bougie group versus patients randomized to the endotracheal tube with stylet group with regard to the primary outcome of successful intubation on the first attempt. The difference in proportion and the associated 95% confidence interval will be presented; between group differences will be tested using a chi-square comparison.

11.4.2 Secondary Analysis

Unadjusted test of treatment effect. The secondary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to the bougie group versus patients randomized to the endotracheal tube with stylet group regarding the secondary outcome of severe hypoxemia (lowest oxygen saturation < 80%). The difference in proportion and the associated 95% confidence interval will be presented; between group differences will be tested using a chi-square comparison.

11.4.3 Exploratory Analyses

Analysis of Exploratory Outcomes. We will conduct unadjusted, intention-to-treat analyses comparing patients randomized to the bougie group to patient randomized to the endotracheal tube with stylet group with regard to pre-planned subgroup and exploratory outcomes. Continuous outcomes will be compared with the Wilcoxon rank sum test and categorical variables with the chi-square test. Between-group differences in continuous and categorical variables and the associated 95% confidence intervals will be presented.

Heterogeneity of Treatment Effect. Exploratory analyses will be conducted to examine whether pre-specified variables modify the effect of bougie vs endotracheal tube stylet use on the primary outcome using multivariable logistic regression with a formal test of interaction. Proposed effect modifiers include:

- Operator Experience
    - Total number of previous intubations performed by operator
    - Number of previous intubations performed by operator with a bougie
- Location (Emergency Department vs Intensive Care Unit)
- Presence of a difficult airway characteristic (to be analyzed in composite and separately):
    - body fluids obscuring glottic view
    - obesity (BMI> 30 kg/m^2)
    - cervical immobilization
    - facial trauma
    - airway obstruction or edema
- Laryngoscope type: Direct laryngoscope (without video capability) vs video laryngoscope (with video capability)

Per-Protocol Analysis of Primary Outcome. In addition to the intention-to-treat analysis, we will conduct a per-protocol analysis comparing the primary outcome between intubations where a bougie was used on the first attempt at intubation and intubations where a bougie was not used on the first attempt at intubation.

Handling of Missing Data: The primary analysis will be limited complete case analysis. There will be no imputation of missing data for the primary analysis of the primary or secondary outcomes.

Interim Analysis:

The DSMB will conduct a single interim analysis for efficacy at the anticipated halfway point of the trial, after enrollment of 553 patients. The stopping boundary for efficacy will be met if the P value for the difference in the incidence of the primary outcome (successful intubation on the first attempt) between groups using a chi-square test is 0.001 or less. Using this conservative Haybittle–Peto boundary ($P \leq 0.001$) will allow the final analysis to be performed using an unchanged level of significance.

The DSMB will also formally evaluate the safety of the trial at the interim analysis. The DSMB will review the incidence of esophageal intubation and airway trauma. Using a chi-square test, if the *P* value for the difference between study groups in either variable is 0.025, it is recommended that the study be stopped early for safety. Additionally, the DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

12 Privacy and Confidentiality

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities

will be collected. All patients will be assigned a unique study ID number for tracking. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. REDCap tools will be used to ensure that the minimal PHI that is collected will be visible only to site investigators at the site where the patient was enrolled, and additional tools will be use to ensure that only deidentified data can be exported from the online database for analysis.

13 Follow-up and Record Retention

Patients will be followed after enrollment for 28 days or until hospital discharge, whichever occurs first. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

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Clinical Trial Protocol

Study Title	Bougie or Stylet In Patients Undergoing Intubation Emergently (BOUGIE): a randomized, multi-center trial
Acronym	BOUGIE
Version	Version 1.2
Date	January 16, 2020
Protocol Co-Chairs	Brian Driver MD Assistant Professor of Emergency Medicine Hennepin County Medical Center and University of Minnesota Matthew Prekker MD, MPH Assistant Professor of Emergency Medicine and Pulmonary and Critical Care Medicine Hennepin County Medical Center and University of Minnesota
Coordinating Center	Vanderbilt University Medical Center Director: Jonathan D. Casey MD ED Site Director: Wesley H. Self, MD, MPH ICU Site Director: Todd W. Rice, MD, MSc
Network	Pragmatic Critical Care Research Group (PCCRG) Steering Committee Chair: Matthew W. Semler MD, MSc

Table of Contents

Trial Summary

Title: Bougie or stylet in patients undergoing intubation emergently (BOUGIE) trial. A randomized trial of bougie use on the first intubation attempt to improve the safety and efficiency of tracheal intubation among critically ill adults.

Background: Complications are common during tracheal intubations performed outside of the operating room. Successful intubation on the first attempt has been associated with a lower rate of procedural complications, but the proportion of critically ill patients intubated on the first attempt during tracheal intubations outside of the operating room is less than 90%. The bougie, a thin semi-rigid tube that can be placed into the trachea, allowing a Seldinger-like technique of intubating a patient's airway, has been traditionally reserved for difficult or failed airways. However, a recent single center trial of adult patients intubated in an emergency department demonstrated that use of the bougie on the first attempt improved intubation success, compared to use of a traditional stylet. We propose a multi-center randomized trial to compare first-attempt bougie use versus endotracheal tube with stylet use for tracheal intubation of critically ill adults in the ED and ICU.

Primary aim: To compare the effect of bougie use versus endotracheal tube with stylet use on the incidence of successful intubation on the first attempt among adults undergoing urgent or emergent tracheal intubation.

Secondary aim: To compare the effect of bougie use versus endotracheal tube with stylet use on the incidence of severe hypoxemia among adults undergoing urgent or emergent orotracheal intubation.

Primary hypothesis: Bougie use will increase the incidence of successful intubation on the first attempt among adults undergoing urgent or emergent intubation

Secondary hypothesis: Bougie use will decrease the incidence of severe hypoxemia among adults undergoing urgent or emergent intubation

Inclusion criteria:

6. Patient is located in a participating unit of an adult hospital
7. Planned procedure is tracheal intubation with sedative administration (or tracheal intubation without sedative administration in patients with decreased level of consciousness, cardiac arrest, or respiratory arrest)
8. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit
9. Planned laryngoscopy device is a non-hyperangulated laryngoscope blade

Exclusion criteria:

7. Patient is pregnant
8. Patient is a prisoner
9. Urgency of intubation precludes safe performance of study procedures

10. Operator feels an approach to intubation other than use of a bougie or use of an endotracheal tube with stylet would be best for the care of the patient
11. Operator feels use of a bougie is required or contraindicated for the care of the patient
12. Operator feels use of an endotracheal tube with stylet is required or contraindicated for the care of the patient

Consent: Given that use of a bougie and use of an endotracheal tube with stylet are both routine approaches during the first attempt at tracheal intubation in the ED and ICU; the lack of established risk or benefit with either approach; and the impracticability of obtaining informed consent prior to urgent or emergent tracheal intubation among critically ill patients, a waiver of informed consent will be requested.

Randomization: Using opaque envelopes available in participating units, participants will be randomized 1:1 to use of a bougie versus use of an endotracheal tube with stylet on the first intubation attempt.

Study interventions:

3. Bougie: a straight, semi-rigid, disposable bougie > 60 cm in length will be used to intubate the trachea during laryngoscopy, then an assistant will load an appropriately-sized endotracheal tube over the bougie and the operator will advance the tube over the bougie into the trachea.
4. Endotracheal tube with stylet: an endotracheal tube with pre-loaded malleable stylet will be used to intubate the trachea during laryngoscopy.

Primary outcome:
Successful intubation on the first attempt

Secondary outcome:
Incidence of severe hypoxemia (lowest arterial oxygen saturation between induction and two minutes following intubation of less than 80%). Induction is defined as when the sedative agent is administered.

Exploratory outcomes:

- Cormack-Lehane grade of glottic view
- Number of laryngoscopy attempts
- Number of attempts at passing bougie
- Number of attempts at passing endotracheal tube
- Duration of intubationOperator-assessed difficulty of intubation
- Whether the video laryngoscope screen was viewed
- Incidence of mechanical intubation complications, including:
    - Esophageal intubation
    - Airway injury
    - Aspiration noted during the intubation attempt
- Cardiac arrest within 1 hour following intubation
- Incidence of peri-intubation cardiovascular collapse defined as any of:

    - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation
    - New or increased vasopressor between induction and 2 minutes following intubation
    - Cardiac arrest within 1 hour following intubation
    - Death within 1 hour following intubation
- ICU-free days in the first 28 days
- Ventilator free days in the first 28 days
- 28-day all-cause in-hospital mortality

1 Background

Tracheal intubation of critically-ill adults is frequently performed in the Emergency Department (ED) and Intensive Care Unit (ICU). Successful intubation on the first attempt has been associated with reduced peri-intubation complications.[1] However, less than 90% of patients are intubated on the first attempt in most settings outside of the operating room, highlighting an opportunity for improvement.[2,3]

Tracheal intubation involves the administration of procedural medications (induction), use of a direct or video laryngoscope to obtain a view of the glottic structures (laryngoscopy), and passage of an endotracheal tube through the vocal cords (intubation). The final step of the procedure, intubation, may be performed by passing a bougie (a disposable tracheal tube introducer of approximately 70 cm in length) through the vocal cords and then passing an endotracheal tube over the bougie and into the trachea, or by directly placing an endotracheal tube (preloaded with a malleable stylet) into the trachea. It is unknown whether using a bougie or an endotracheal tube with stylet is more likely to result in successful placement of an endotracheal tube in the trachea on the first attempt at laryngoscopy and intubation. Some providers routinely use a bougie on the first attempt, with studies reporting the use of a bougie during the first intubation attempt in up to 80% of procedures.[4] Other providers most commonly use an endotracheal tube with stylet on the first attempt, reserving the bougie as a backup device in cases of suboptimal laryngoscopic view, with other studies reporting the use of a bougie in less than 5% of intubation attempts.[2]

Only one prior randomized trial has compared use of a bougie versus endotracheal tube with stylet for tracheal intubation outside of the operating room. This single-center trial found a significantly higher rate of first attempt intubation success with bougie use (98%) compared to the endotracheal tube with stylet (87%) in adult patients undergoing emergent tracheal intubation in the ED.[5] There were no differences between the two groups in rates of complications or clinical outcomes. Operators in this single-center trial had substantial familiarity with the bougie. This device was used on the first intubation attempt in approximately 80% of procedures before the trial began.[4] It is unknown if these results will generalize to other settings where operators use the bougie less frequently than the may have less experience with the use of a bougie and more experience with using an endotracheal tube with stylet.

2 Rationale, Aims, and Hypotheses

To determine if the use of a bougie increases the incidence of successful intubation on the first attempt in a broad variety of practice settings among a population of operators with varied prior experience with bougie and endotracheal tube with stylet, a multi-center randomized trial is needed.

2.1 Study Aims

- Primary:

- To compare the effect of bougie use versus endotracheal tube with stylet use on successful intubation on the first attempt among adults undergoing urgent or emergent tracheal intubation

- Secondary:
  To compare the effect of bougie use versus endotracheal tube with stylet use on the incidence of severe hypoxemia (lowest arterial oxygen saturation between induction and two minutes following intubation of less than 80%). Induction is defined as when the sedative agent is administered.

2.2 Study Hypotheses

- Primary:
  - Bougie use will increase the incidence of successful intubation on the first attempt among adults undergoing urgent or emergent intubation

- Secondary
  - Bougie use will decrease the incidence of severe hypoxemia among adults undergoing urgent or emergent intubation

3 Study Description

To address these aims, we propose a multi-center, non-blinded, parallel-group, randomized clinical trial evaluating the effect of using a bougie versus using an endotracheal tube with stylet on successful intubation on the first attempt. Patients located in participating EDs and ICUs who are deemed by the treating physicians to require tracheal intubation and who are appropriate according to inclusion/exclusion criteria will be enrolled and randomly assigned to bougie use versus endotracheal tube with stylet use on the first intubation attempt. All other decisions regarding airway management will remain at the discretion of the treating physician. Data will be prospectively collected at the time of intubation by an independent observer and supplemented with review of the medical record to determine the effect of the assigned interventions on study outcomes.

4 Study Population, Inclusion and Exclusion Criteria

4.1 Study Population

The study population will be critically-ill adults for whom the clinical team has elected to perform tracheal intubation via the oral route using a non-hyperangulated blade (Macintosh or Miller-style). To be eligible for enrollment, the patient must meet all inclusion criteria and none of the exclusion criteria.

4.2 Inclusion Criteria

6. Patient is located in a participating unit of an adult hospital
7. Planned procedure is tracheal intubation with sedative administration (or tracheal intubation without sedative administration in patients with decreased level of consciousness, cardiac arrest, or respiratory arrest)
8. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit
9. Planned laryngoscopy device is a non-hyperangulated laryngoscope blade

Examples of qualifying laryngoscope blades include: traditional Miller blade and handle; traditional Macintosh laryngoscope blade and handle; Medtronic McGrath™ MAC Video Laryngoscope; KARL STORZ C-MAC® Video Laryngoscope; GlideScope MAC S3 & S4 blades or T3/4

Examples of non-qualifying laryngoscope blades include: GlideScope Ranger; GlideScope AVL™; KARL STORZ C-MAC D-Blade

4.3 Exclusion Criteria

Exclusion criteria:

7. Patient is pregnant
8. Patient is a prisoner
9. Urgency of intubation precludes safe performance of study procedures
10. Operator feels an approach to intubation other than use of a bougie or use of an endotracheal tube with stylet would be best for the care of the patient
11. Operator feels use of a bougie is required or contraindicated for the care of the patient
12. Operator feels use of an endotracheal tube with stylet is required or contraindicated for the care of the patient

5 Enrollment and Randomization

5.1 Study Sites:

1. Participating intensive care units
2. Participating emergency departments

5.2 Enrollment

All patients will be enrolled at the time the clinical team elects to intubate and the patient meets all inclusion criteria but no exclusion criteria. Patients who are enrolled but have a change in clinical status precluding intubation (e.g. resolution of respiratory failure or death prior to procedure) will be prospectively recorded.

5.3 Consent

Intubation using a bougie and intubation using an endotracheal tube with stylet are both accepted practice in urgent or emergent intubation in adults. Currently, there are no evidence-based guidelines to inform practice in this area, and there is significant variation in practice between providers.

Patients requiring intubation in the ED or ICU are critically ill and are at significant risk for morbidity and mortality as a result of their underlying illness. Moreover, each patient undergoing intubation in routine clinical care receives intubation using either a bougie or an endotracheal tube with stylet on the first attempt. Thus, the benefits or risks of these two approaches are experienced by patients undergoing intubation in clinical care, outside the context of research. For every patient enrolled in the proposed trial, the treating clinicians specifically feels that either a bougie or an endotracheal tube with stylet would be a safe approach for the patient (otherwise the patient is excluded). Therefore, making the decision between the two approaches randomly (by study group assignment) rather than by a provider who thinks either approach is safe for the patient, is felt by the investigators to pose minimal additional risk.

In summary, because both approaches to tracheal intubation being studied are (1) commonly used as a part of routine care, (2) are interventions to which the patient would likely be exposed even if not participating in the study, and (3) are acceptable options from the perspective of the treating clinicians (otherwise the patient is excluded), and (4) there are no established risk or benefit with either approach, we feel the study meets criteria for minimal risk.

Additionally, obtaining informed consent in the study would be impracticable. Tracheal intubation of acutely ill patients is a time-sensitive procedure. Despite the availability of a formal informed consent document for the procedure itself, time allows discussion of risks and benefits in less than 10% of airway management events in the study settings.

Because the study poses minimal risk, would not adversely affect the welfare or privacy rights of the participant, and consent would be impracticable, we will request a waiver of informed consent.

Previous randomized trials comparing two standards of care for emergency intubation have been completed under a waiver of informed consent.[5–12]

Information regarding the study will be made available to patients and families by one of three mechanisms: (1) a patient and family notification sheet provided to each patient and family following enrollment informing the patient of his or her enrollment and describing the study, (2) a patient and family information sheet posted in at least three publicly-visible locations within the study unit containing general information about the study and contact information for the research team for additional questions or concerns, (3) a patient and family information sheet provided to each patient and family on admission as part of an "admission packet" containing general study information and contact information for the research team for additional questions or concerns. Which mechanism of providing information to patients and families will be used at each study site will be determined by site investigators in coordination with the local context assessment of the site IRB.

5.4 Randomization

After enrollment, patients will be randomized in a 1:1 ratio to undergo intubation using a bougie or using an endotracheal tube with stylet for the first attempt. The randomization will be performed using permuted blocks of two, four, and six. The randomization will be stratified by study site (each participating ED and ICU is a different stratum). The study assignments will be placed in opaque randomization envelopes and will be available to operators in participating units. Study group assignment will remain concealed to study personnel and operators until after the decision has been made to enroll the patient in the study and the operator has declared their choice of laryngoscope.

6 Study Procedures

6.1 Study Interventions

The study group assignment will determine only the first device that the operator will attempt to use to intubate the trachea (bougie or endotracheal tube with stylet).

Prior to opening the randomization envelope and revealing the study assignment, the operator will select a laryngoscope with a non-hyperangulated curved blade and will indicate their selection by circling the name of the laryngoscope on the front of the randomization envelope.

After selecting a laryngoscopy device, and receiving study group assignment, the operator will proceed with the procedure. All other aspects of the intubation procedure will be at the discretion of the operator, including endotracheal tube diameter, patient position, pre-oxygenation, approach to ventilation and oxygenation during intubation, and any devices used following the first intubation attempt. Use of video assistance during direct laryngoscopy, if available, is a dynamic decision during the procedure and will be at the discretion of the operator for any selected device capable of video assistance.

Although the study assignment stipulates the first device for intubating the trachea, if there are difficulties with intubation the operator is free to use any other method of intubation, including crossover to the other treatment group. Tracheal intubation will be confirmed with capnography.

6.1.1 Bougie Group

This trial seeks to evaluate the use of straight, semi-rigid bougies because they are likely to be more effective than less-rigid bougies packaged in a curled position. The latter type of bougie may be more difficult to advance through the glottic opening.[13] The BEAM trial found an absolute between-group difference of 11% for first attempt success, favoring the group intubated with a 70 cm, semi-rigid, malleable, straight bougie with a coude tip (SunMed). Therefore, participating units will use a straight bougie at least 60 cm in length; a coude tip is favored but not required. Operators may choose whether and how to bend the bougie prior to intubation.

In the bougie group, the operator will attempt to pass the bougie into the trachea. If successful, an assistant will load the endotracheal tube (no stylet) over the bougie and the operator, without removing the laryngoscope from the mouth, will guide the tube through the vocal cords to the desired depth in the trachea. If resistance is encountered when passing the endotracheal tube over the bougie (presumably from the bevel-tip of the tube catching on the arytenoid cartilages), the tube will be retracted 2 centimeters, rotated 90° counterclockwise, and readvanced into the trachea. It is acceptable but not encouraged to pre-load the endotracheal tube onto the bougie before intubating the trachea. An assistant will remove the bougie from within the endotracheal tube prior to manual ventilation and capnographic confirmation. During bougie removal, the operator must hold the tube firmly in the desired tracheal position to avoid inadvertent tracheal extubation. If the bougie is not successfully placed in the trachea or the endotracheal tube successfully advanced over the bougie on the first attempt at intubation, the operator may use any approach to additional attempts at tracheal intubation.

6.1.2 Endotracheal tube with stylet use

In the endotracheal tube with stylet group, the operator will attempt to intubate the trachea with an endotracheal tube containing a removeable, malleable stylet. Manipulation of the shape/curve of the endotracheal tube with stylet is at the discretion of the operator before the first intubation attempt, however a "straight-to-cuff" shape and a bend angle of 25° to 35° is encouraged. If difficulty in passage is encountered, the operator can withdraw, rotate, or reshape the tube and stylet as needed. The stylet will be left in place until the tube is advanced to the trachea.

6.1.3 Operator training

An online training video summarizing best practices in use of both the bougie and endotracheal tube with stylet will be made available to all operators at participating units. Before trial enrollment begins, operators routinely expected to perform tracheal intubation in each unit will attest to viewing the online training video. In addition, the randomization sheet will contain reminders of best-practices for each group.

The randomization sheet for the bougie group will suggest that:

3. Following placement of the bougie in the trachea, an assistant should load the endotracheal tube (no stylet) over the bougie
4. The laryngoscope should remain in place while the operator advances the endotracheal tube over the bougie, rotating the tube 90° counterclockwise as it passes the vocal cords

The randomization sheet for the endotracheal tube with stylet group will suggest that:

3. A "straight-to-cuff" shape and a bend angle of 25° to 35° is encouraged (with a stock photo demonstrating the suggested shape).
4. If intubation is difficult or unsuccessful, the operator can withdraw, reshape, or rotate the tube as needed

7 Data Collection and Outcome Measures

7.1 Data Collection

All data are collected non-invasively as a part of current usual care. No additional data will be obtained beyond that which is obtained by bedside observation and from the electronic medical record.

Important peri-procedural outcomes will be captured by an independent, in-person observer not participating in the tracheal intubation procedure. These independent observers will be trained and use standardized data collection forms. They will be responsible for capturing the primary endpoint for this trial, successful intubation on the first attempt. To ensure a standardized application of the endpoint definition, an online instructional video will be created explaining how to record the number of attempts. The video will demonstrate the scoring process in several example intubation procedures, performed by the principal investigators using both the bougie and the endotracheal tube with stylet. This video will be available to all independent observers throughout the procedure.

The following variables will be recorded:

Baseline: Age, gender, height, weight, body mass index, race, APACHE II score, active medical problems at the time of intubation, active comorbidities complicating intubation, vasopressor use prior to intubation, noninvasive ventilator use, high flow nasal cannula use, highest FiO_2 delivered in prior 6 hours, indication for intubation, reintubation within 72 hours of extubation, preoxygenation technique, and operator experience.

Peri-procedural: Date and time of sedative administration, oxygen saturation and systolic blood pressure at time of sedative administration, lowest arterial oxygen saturation from induction to two minutes after intubation, lowest and highest systolic blood pressure from induction to two minutes after intubation, vasopressor administration, duration of intubation, number of times a laryngoscope entered the mouth, number of times a bougie entered the mouth, and number of times an endotracheal tube entered the mouth will be collected by a trained, independent observer not affiliated with the performance of the procedure. Sedative agent name and dose, neuromuscular blocking agent name and dose, use of bag-valve-mask ventilation, laryngoscope type, best Cormack-Lehane glottic view on the first attempt, percent of glottic opening, viewing the screen of a videolaryngoscope during the first attempt, total number of attempts, presence of aspiration between induction and intubation, rescue device use, need for additional operators, presence of predictors of difficult laryngoscopy (body fluids obscuring glottic view, cervical immobilization, facial trauma, airway obstruction or edema), and mechanical complications (esophageal intubation, airway trauma) will be obtained from the operator. Additional outcomes of the airway procedure will be obtained from retrospective chart review.

0-24 hours: Post-intubation shock or cardiac arrest, post-intubation pneumothorax, oxygen saturation, FiO_2, PEEP, and mean arterial pressure at 24 hours after intubation.

In-Hospital Outcomes: Ventilator-free days, ICU-free days, date of death

7.2 Outcome Measures

7.2.1 Primary Outcome

The primary outcome is successful intubation on the first attempt. Successful intubation on the first attempt is defined as placement of an endotracheal tube in the trachea (confirmed by standard means including capnography) following: (1) a single insertion of a laryngoscope blade into the mouth and (2) EITHER a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube into the mouth OR a single insertion of an endotracheal tube with stylet into the mouth.

7.2.2 Secondary Outcome

The secondary trial outcome is the incidence of severe hypoxemia. Severe hypoxemia is defined as an oxygen saturation less than 80% during the time interval from induction to two minutes after completion of the intubation procedure.

7.2.3 Exploratory Outcomes

- Cormack-Lehane grade of glottic view
- Number of laryngoscopy attempts
- Number of attempts at passing bougie
- Number of attempts at passing endotracheal tube
- Duration of intubation – The start of the procedure will be defined as the first of sedative administration or initiation of laryngoscopy. The end of the procedure will be defined as the time of the final placement of an endotracheal tube or tracheostomy tube in the trachea.
- Operator-assessed difficulty of intubation
- Whether the video laryngoscope screen was viewed
- Incidence of mechanical intubation complications, including:
    - Esophageal intubation
    - Aspiration noted during the intubation attempt
    - Airway trauma
- Cardiac arrest within 1 hour following intubation
- Incidence of peri-intubation cardiovascular collapse defined as any of:
    - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation
    - New or increased vasopressor between induction and 2 minutes following intubation
    - Cardiac arrest within 1 hour following intubation
    - Death within 1 hour of following intubation
- ICU-free days in the first 28 days
- Ventilator free days in the first 28 days
- 28-day all-cause in-hospital mortality

8 Risks and Benefits

Both bougie use and endotracheal tube with stylet use are both accepted standards of care. Both approaches to intubation are routinely used in the study units. There are no known risk differences between the two intubation modalities. In the only randomized trial comparing these intubation strategies, there were no differences in clinical outcomes or complications. For this reason, there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by critically ill patients requiring tracheal intubation as part of routine care. The societal benefit of this study could be substantial in the form of improved understanding of safe and effective airway management outside of the operating room.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. REDCap tools will be used to ensure that the PHI that is collected is only visible to investigators at the healthcare system where the patient as enrolled. To protect participant privacy, REDCap tools will be used to ensure that only deidentified data can be exported for use during analysis.

9 Safety Monitoring and Adverse Events

9.1 Safety Monitoring

The study will take place in EDs and ICUs at the time of a procedure required for routine clinical care. Thus, at the time of study intervention, the patient will have in the room: a physician trained in the care of critically ill adults, a critical care or emergency medicine nurse, and usually a respiratory therapist. The patient will be receiving continuous invasive or non-invasive monitoring. Any and all complications, whether or not related to the study, will be cared for in real-time by these physicians. Additionally, if at any point the treating team believes it is unsafe to use either the bougie or endotracheal tube with stylet, the study intervention will be halted and the patient will be intubated in the manner deemed safest by the treating team.

A Data and Safety Monitoring Board (DSMB) will oversee the trial. Interim analyses for safety and efficacy will be conducted as described in the Statistical Analysis section of the protocol.

10.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation participant administered an intervention that does not necessarily have to have a causal relationship with this treatment. An adverse event therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an intervention, whether or not the incident is considered related to the intervention.

A serious adverse event (SAE) is defined as any unexpected and untoward medical occurrence that meets any of the following criteria:

8. Results in death
9. Is life threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
10. Requires inpatient hospitalization
11. Prolongs an existing hospitalization
12. Results in persistent or significant disability or incapacity
13. Results in a congenital anomaly or birth defect
14. Important medical event that requires an intervention to prevent any of 1-6 above.

The overall principal investigator and site principal investigators will be responsible for overseeing the safety of this trial on a daily basis. They will be available any time for questions from the clinical team, who will also be monitoring the patients continuously for adverse events and serious adverse events. Serious and unexpected adverse events potentially associated with study interventions will be recorded in a case report form in the study record and promptly reported to the IRB. As tracheal intubation in the critical care setting is known to be independently associated with numerous adverse events including failed attempts at intubation, esophageal intubation, arterial oxygen desaturation, aspiration, hypotension, cardiac arrest, and death, these events will be continuously monitored by study personnel to determine if a preponderance of adverse events in one study group merits stoppage of the trial. However, in the absence of an imbalance of the above events between study groups, these events are expected in the routine performance of the airway management procedure and will not be individually recorded and reported to the IRB as unexpected adverse events.

Communication and Reporting of Adverse Events. In order to ensure proper and timely reporting of all adverse events, there will be a clear communication plan for all study personnel to follow. Serious and unexpected adverse events potentially associated with study interventions will be reported to the PI within 72 hours of occurrence and recorded in a case report form in the study record. The PI will, in turn, report all SAEs potentially related to study procedures to the IRB and DSMB within 7 calendar days of occurrence in accordance with IRB policy

As an additional safety measure, the exclusion criteria specifically state that airway management events in which the operator foresees the potential need for a specific intubation device (bougie, endotracheal tube with stylet, or other) will not be included in the trial so all airway management events studied will be those in which the treating clinical felt equipoise between the interventions being examined. Further, only the initial intubating device is proscribed by the study protocol and if at any time during the procedure the operator chooses to employ an alternative airway management strategy they are free to do so.

In addition, a DSMB containing at least one clinical investigator experienced in monitoring and conducting clinical trials in critically ill patients will oversee the study. In addition to assisting the PI with monitoring the trial for safety, the DSMB will also perform the interim analyses described in the statistical methods. If the data meet the stopping rules for efficacy at the interim

analysis, the DSMB will communicate a recommendation to stop the trial at that time. In addition, the DSMB will also be available to review unexpected serious adverse events in a timely manner. They will be asked to be available for rapid access by the investigators in the case of the need to evaluate unexpected serious adverse events or any other major unanticipated or safety related issues. Furthermore, in cases of unexpected serious adverse events, the DSMB will have the ability to pause the trial to investigate possible safety issues and/or suggest changes to the design of the study to abrogate any safety issues.

10.3 Study Withdrawal

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI.

The reason and date of every withdrawal will be recorded in the patient study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or other safety parameter that could have led to discontinuation. Follow-up will be conducted until the condition has resolved, until diagnosis of the adverse event or safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well.

11 Statistical Considerations

11.1 General Considerations

We will present summary tabulations by treatment group. For categorical variables, the number and percentage of patients within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of patients, mean or median as appropriate, and standard deviation or interquartile range as appropriate, will be presented.

Formal statistical hypothesis testing will be performed on the primary and secondary outcomes, with all tests conducted at the 2-sided, 0.05 level of significance.

11.2 Sample Size Estimation

A prior single-center randomized trial reported an absolute difference of 11% in successful intubation on the first attempt between the bougie and endotracheal tube with stylet groups. Because this trial occurred in an ED that was already familiar with bougie use, the difference in successful intubation on the first attempt that could be achieved in other settings may be of lesser magnitude. Additionally, successful intubation on the first attempt in intensive care units has traditionally been lower than in ED settings.[2,3,10,11] Therefore, the current trial will be designed to detect a 6% absolute difference between groups in the incidence of successful intubation on

the first attempt. Assuming an incidence of successful intubation on the first laryngoscopy attempt of 84% in the endotracheal tube with stylet group, detecting a 6% absolute increase in the incidence of successful intubation on the first attempt with 80% power at a two-sided alpha level of 0.05 would require enrollment of 1,050 patients (525 per group). Anticipating missing data for 5% of patients or less, we will plan to enroll a total of 1,106 patients (553 per group).

This sample size calculation was performed in STATA version 15.1 with the following command: sampsi 0.90 0.84, p(0.8).

11.3 Analysis Populations

The intent-to-treat (ITT) population will be the primary outcome analysis population. Patients who meet any exclusion criterion will not be a part of the ITT population and will be considered screening failures.

11.4 Statistical Analysis

Prior to the conclusion of enrollment, we will make publicly available a complete final statistical analysis plan. Analyses conducted in accordance with the statistical analysis plan will be identified as *a priori*. Any additional analyses requested by the investigators or reviewers will be identified as *post hoc*.

11.4.1 Primary Analysis

Unadjusted test of treatment effect. The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to the bougie group versus patients randomized to the endotracheal tube with stylet group with regard to the primary outcome of successful intubation on the first attempt. The difference in proportion and the associated 95% confidence interval will be presented; between group differences will be tested using a chi-square comparison.

11.4.2 Secondary Analysis

Unadjusted test of treatment effect. The secondary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to the bougie group versus patients randomized to the endotracheal tube with stylet group regarding the secondary outcome of severe hypoxemia (lowest oxygen saturation < 80%). The difference in proportion and the associated 95% confidence interval will be presented; between group differences will be tested using a chi-square comparison.

11.4.3 Exploratory Analyses

Analysis of Exploratory Outcomes. We will conduct unadjusted, intention-to-treat analyses comparing patients randomized to the bougie group to patient randomized to the endotracheal tube with stylet group with regard to pre-planned subgroup and exploratory outcomes. Continuous outcomes will be compared with the Wilcoxon rank sum test and categorical

variables with the chi-square test. Between-group differences in continuous and categorical variables and the associated 95% confidence intervals will be presented.

Heterogeneity of Treatment Effect. Exploratory analyses will be conducted to examine whether pre-specified variables modify the effect of bougie vs endotracheal tube stylet use on the primary outcome using multivariable logistic regression with a formal test of interaction. Proposed effect modifiers include:

- Operator Experience
    - Total number of previous intubations performed by operator
    - Number of previous intubations performed by operator with a bougie
- Location (Emergency Department vs Intensive Care Unit)
- Presence of a difficult airway characteristic (to be analyzed in composite and separately):
    - body fluids obscuring glottic view
    - obesity (BMI> 30 kg/m^2)
    - cervical immobilization
    - facial trauma
    - airway obstruction or edema
- Laryngoscope type: Direct laryngoscope (without video capability) vs video laryngoscope (with video capability)

Per-Protocol Analysis of Primary Outcome. In addition to the intention-to-treat analysis, we will conduct a per-protocol analysis comparing the primary outcome between intubations where a bougie was used on the first attempt at intubation and intubations where a bougie was not used on the first attempt at intubation.

Handling of Missing Data: The primary analysis will be limited complete case analysis. There will be no imputation of missing data for the primary analysis of the primary or secondary outcomes.

Interim Analysis:

The DSMB will conduct a single interim analysis for efficacy at the anticipated halfway point of the trial, after enrollment of 553 patients. The stopping boundary for efficacy will be met if the P value for the difference in the incidence of the primary outcome (successful intubation on the first attempt) between groups using a chi-square test is 0.001 or less. Using this conservative Haybittle–Peto boundary ($P \leq 0.001$) will allow the final analysis to be performed using an unchanged level of significance.

The DSMB will also formally evaluate the safety of the trial at the interim analysis. The DSMB will review the incidence of esophageal intubation and airway trauma. Using a chi-square test, if the *P* value for the difference between study groups in either variable is 0.025, it is recommended that the study be stopped early for safety. Additionally, the DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

12 Privacy and Confidentiality

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. REDCap tools will be used to ensure that the minimal PHI that is collected will be visible only to site investigators at the site where the patient was enrolled, and additional tools will be use to ensure that only deidentified data can be exported from the online database for analysis.

13 Follow-up and Record Retention

Patients will be followed after enrollment for 28 days or until hospital discharge, whichever occurs first. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

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Bougie or Stylet In Patients Undergoing Intubation Emergently (BOUGIE) trial

Study Protocol Revision Sequence

4/19/2019 Original protocol, version 1.0
4/29/2019 First patient enrolled
7/2/2019 **Amendment to Study Protocol, version 1.1**

The inclusion criteria were clarified to specify that patients could be enrolled without a sedative in cases of decreased level of consciousness, cardiac arrest, or respiratory arrest (only cardiac arrest has been specified in the initial protocol)

The definition of duration of intubation was clarified. The start of the procedure is defined as the first of sedative administration or initiation of laryngoscopy, and the end of the procedure is defined as the time of the final placement of an endotracheal tube or tracheostomy tube in the trachea.

Minor changes to the definitions of outcomes to match the versions registered in clinicaltrials.gov

1/16/2020 **Amendment to Study Protocol, version 1.2**

The current inclusion/exclusion criteria state that patients would be excluded for age < 18. Occasionally, patients present to emergency department or intensive care unit with unknown identities and ages and an inability to communicate. If the patient has the gross appearance of an adult and is brought to an adult hospital, they may be emergently intubated and enrolled in the study before they can be identified as less than 18 years of age. In this revision, the enrollment criteria for age has been removed and replaced with a criteria specifying that the patient must be located in an adult hospital.

2/14/2021 Enrollment completed

BOugie or stylet in patients UnderGoing Intubation Emergently (BOUGIE): protocol and statistical analysis plan for a randomized clinical trial

Brian E Driver*, MD[1]; Matthew W Semler*, MD, MSc[2]; Wesley H Self, MD[3], MPH; Adit A Ginde, MD, MPH[4]; Sheetal Gandotra, MD[5]; Stacy A Trent, MD, MPH[4,6]; Lane M Smith, MD, PhD[7]; John P Gaillard, MD[7]; David B Page, MD[8,9]; Micah R Whitson, MD[8,9]; Derek J Vonderhaar, MD[10]; Aaron M Joffe, DO, FCCM[11]; Jason R West, MD[12]; Christopher G Hughes, MD, MS[13]; Janna S Landsperger, MS, PA-C[2]; Michelle P Howell, RN, BSN[4]; Derek W Russell, MD[5]; Swati Gulati, MBBS, MS[5]; Itay Bentov, MD, PhD[11]; Steven H Mitchell, MD[14]; Andrew J Latimer, MD[14]; Kevin Doerschug, MD[15]; Kevin Gibbs, MD[16]; Li Wang, MS[17]; Christopher J Lindsell, PhD[17]; David R Janz, MD, MSc[18]; Todd W Rice, MD[2]; Matthew E Prekker**, MD MPH[1,19]; Jonathan D Casey**, MD, MSc[2]
for the BOUGIE Investigators# and the Pragmatic Critical Care Research Group.

*Authors contributed equally

** Authors contributed equally

#See below for a full list of the BOUGIE Investigators

1. Hennepin County Medical Center, Department of Emergency Medicine, Minneapolis, MN
2. Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Nashville, TN
3. Vanderbilt University School of Medicine, Department of Emergency Medicine, Nashville, TN
4. University of Colorado School of Medicine, Department of Emergency Medicine, Aurora, CO
5. University of Alabama at Birmingham, Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine; Birmingham Veteran's Affairs Medical Center, Pulmonary Section, Birmingham, AL
6. Denver Health Medical Center, Department of Emergency Medicine, Denver, CO
7. Wake Forest Baptist Health, Department of Emergency Medicine, Winston-Salem, NC
8. University of Alabama at Birmingham, Department of Emergency Medicine, Birmingham, AL
9. University of Alabama at Birmingham, Department of Medicine, Division of Pulmonary, Allergy & Critical Care Medicine, Birmingham, AL
10. Ochsner Health System New Orleans, Department of Pulmonary and Critical Care Medicine, New Orleans, LA
11. University of Washington, Department of Anesthesiology and Pain Medicine, Seattle, WA
12. Lincoln Medical Center, Department of Emergency Medicine, Bronx, NY
13. Vanderbilt University Medical Center, Department of Anesthesiology, Nashville, TN
14. University of Washington, Department of Emergency Medicine, Seattle, WA

15. University of Iowa, Department of Internal Medicine, Iowa City, IA
16. Wake Forest School of Medicine, Department of Medicine, Section of Pulmonary, Critical Care, Allergy and Immunologic Disease, Winston-Salem, NC
17. Vanderbilt University Medical Center, Department of Biostatistics, Nashville, TN
18. Louisiana State University School of Medicine New Orleans, Department of Medicine, Section of Pulmonary/Critical Care Medicine and Allergy/Immunology, New Orleans, LA
19. Hennepin County Medical Center, Division of Pulmonary/Critical Care, Department of Medicine, Hennepin County Medical Center

Corresponding Author:

Brian E Driver, MD

Email:

brian.driver@hcmed.org

Address:

Department of Emergency Medicine, Mailcode R2

701 Park Ave

Minneapolis, MN 55415

Author contributions: All study authors approved the final version of this manuscript. Study concept and design: BED, MWS, WHS, DRJ, TWR, MEP, JDC. Acquisition of data: MWS, WHS, AAG, SG, SAT, LMS, JPG, DBP, MRW, DJV, AMJ, JRW, CGH, JSL, MPH, DWR, SG, IB, DRJ, TWR, JDC. Drafting of the manuscript: BED, MWS, MEP, JDC. Critical revision of the manuscript for important intellectual content: BED, MWS, WHS, AAG, SG, SAT, LMS, JPG, DBP, MRW, DJV, AMJ, JRW, CGH, JSL, MPH, DWR, SG, IB, SHM, AJL, KD, KG, LW, CJL, DRJ, TWR, MEP, JDC. Study supervision: BED, MWS, MEP, JDC.

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Abstract:

Introduction: Intubation-related complications are less frequent when intubation is successful on the first attempt. The rate of first attempt success in the ED and ICU is typically less than 90%. The bougie, a semi-rigid introducer that can be placed into the trachea to facilitate a Seldinger-like technique of tracheal intubation and is typically reserved for difficult or failed intubations, might improve first attempt success. Evidence supporting its use, however, is from a single academic emergency department with frequent bougie use. Validation of these findings is needed before widespread implementation.

Methods and Analysis:

The Bougie or Stylet In Patients Undergoing Intubation Emergently (BOUGIE) trial is a prospective, multi-center, non-blinded randomized trial being conducted in 6 EDs and 6 intensive care units in the United States. The trial plans to enroll 1,106 critically-ill adults undergoing orotracheal intubation. Eligible patients are randomized 1:1 to use of a bougie or use of an endotracheal tube with stylet for the first intubation attempt. The primary outcome is successful intubation on the first attempt. The secondary outcome is severe hypoxemia, defined as an oxygen saturation less than 80% between induction until two minutes after completion of intubation. Enrollment began on April 29, 2019 and is expected to be completed in 2021.

Ethics and Dissemination:

The trial protocol was approved with waiver of informed consent by the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at an enrolling site. The results will be submitted for publication in a peer-reviewed journal and presented at scientific conferences.

Trial Registration:

This trial was registered with ClinicalTrials.gov (NCT03928925) on April 26, 2019, prior to the enrollment of the first patient on April 29, 2019.

Strengths and Limitations:

- This ongoing pragmatic trial will compare the rate of successful intubation on the first attempt with use of a bougie versus use of an endotracheal tube with stylet for the first intubation attempt of critically ill adults in the ED or ICU.
- Broad eligibility criteria, diverse prior experience with a bougie among operators, and conduct in the ED and ICU at multiple centers will increase the external validity of the findings.
- Patients, clinicians, and investigators are not blinded to study group assignment after randomization.

Introduction:

Tracheal intubation of critically ill adults is frequently performed in the Emergency Department (ED) and Intensive Care Unit (ICU). Successful intubation on the first attempt has been associated with a lower incidence of peri-intubation complications.[1–4] However, less than 90% of patients are intubated on the first attempt in most settings outside of the operating room, highlighting an opportunity for improvement.[5–7]

Emergency tracheal intubation is commonly performed in three discrete steps. First, medications are administered to facilitate optimal intubating conditions (induction). Second, a laryngoscope is inserted into the patient's mouth and a direct or indirect video view of glottic structures is obtained (laryngoscopy). Third, an endotracheal tube is placed in the mouth and advanced past the vocal cords into the trachea (intubation). Two commonly used devices that aid in placing the endotracheal tube include: a stylet (a malleable, aluminum rod preloaded inside the endotracheal tube to facilitate navigation of the upper airway) or a bougie (a thin, plastic introducer passed into the trachea which serves as a guide for passage of the endotracheal tube). When using a stylet, the endotracheal tube and stylet are passed into the trachea together. When using a bougie, the bougie is first passed into the trachea and then the endotracheal tube is advanced over the bougie using a Seldinger-like technique. There is substantial variation between clinicians as to whether they select the stylet or the bougie for the first intubation attempt.[5,8] For some physicians, the bougie is used primarily as a rescue device in the event difficulty is encountered in laryngoscopy or passage of the endotracheal tube with stylet. Other physicians use a bougie routinely on the first attempt at tracheal intubation.[8,9]

To our knowledge, only one prior randomized trial has compared rates of successful intubation on the first attempt outside of the operating room with use of a bougie versus use of endotracheal tube with stylet: the single-center Bougie Use in Emergency Airway Management (BEAM) trial. That study showed a higher rate of successful intubation on the first attempt with use of a bougie (98%) compared to use of an endotracheal tube with stylet (87%) in adult ED patients (absolute difference 11%, 95% CI 7% to 14%).[10] However, it is possible that these findings reflect increased institution-specific comfort with bougie use compared to the endotracheal tube and

stylet – operators reported using a bougie in approximately 80% of intubations before the trial.[8] It is unknown if the results of the BEAM trial will generalize to other settings where operators have less experience using the bougie and have greater experience using an endotracheal tube with stylet during the first attempt at intubation.

Methods and Analysis:

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see SPIRIT checklist in Supplement fig E1 and Fig. 1).[11]

Patient and Public Involvement

We did not involve patients or the public in the design of the study.

Study Design

The BOugie or Stylet In Patients UnderGoing Intubation Emergently (BOUGIE) trial is a pragmatic, multicenter, unblinded, parallel-group, randomized trial comparing use of a bougie to use of an endotracheal tube with stylet for the first attempt at tracheal intubation among critically ill adults in the ED and ICU. The primary outcome is successful intubation on the first attempt. The trial protocol was approved with waiver of informed consent by the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at an enrolling site. The trial was registered prior to initiation of enrollment (ClinicalTrials.gov identifier: NCT03928925). An independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial. Study sites are listed in the Supplement file, section 7.

Study Population

The inclusion criteria for the trial are:

1. Patient is located in a participating unit of an adult hospital
2. Planned procedure is tracheal intubation with sedative administration (or tracheal intubation without sedative administration in patients with decreased level of consciousness, cardiac arrest, or respiratory arrest)

3. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit
4. Planned laryngoscopy device is a non-hyperangulated laryngoscope blade

The exclusion criteria for the trial are:

1. Patient is pregnant
2. Patient is a prisoner
3. Urgency of intubation precludes safe performance of study procedures
4. Operator feels an approach to intubation other than use of a bougie or use of an endotracheal tube with stylet would be best for the care of the patient
5. Operator feels use of a bougie is required or contraindicated for the care of the patient
6. Operator feels use of an endotracheal tube with stylet is required or contraindicated for the care of the patient

The original inclusion criteria specified that patients must be at least 18 years old to be eligible. With approval from the central institutional review board at Vanderbilt University Medical Center, trial inclusion and exclusion criteria were amended on January 16, 2020 to allow the enrollment of patients less than 18 years of age. Because the identity and age of critically ill patients presenting to the ED are sometimes unknown (e.g., a patient with cardiac arrest presenting by ambulance without family), this criterion was revised to include patients located in a participating unit of an adult hospital. We anticipate that a small number of patients whose identity and age are unknown, who are judged by treating clinicians to be an adult and enrolled in the trial, will later be determined to be less than 18 years old.

Randomization and Treatment Allocation

Patients are randomized in a 1:1 ratio to undergo intubation using a bougie or using an endotracheal tube with stylet for the first attempt in permuted blocks of two, four, or six, stratified by study site. Study-group assignments are generated using a computerized randomization sequence, placed in sequentially numbered opaque envelopes, and

distributed to enrolling sites. Before opening the envelope, the operator determines that the patient meets all inclusion criteria and no exclusion criteria. The operator documents whether they plan to use a video laryngoscope or a direct laryngoscope. The operator then opens the envelope. Patients are considered to be enrolled once the operator opens the envelope to reveal study group assignment. Thus, group assignment is concealed until after documentation of laryngoscope choice and patient enrollment. Patients who are screened and excluded will be reported with trial results using a CONSORT diagram. After enrollment and randomization, patients, treating clinicians, and study personnel are not blinded to study group assignment.

Study Interventions

Training

Before beginning enrollment at a site, operators at each site received a 30-minute in-person lecture and watched a 6-minute training video which demonstrated best-practices for intubation with both a bougie and endotracheal tube with stylet. These materials are available from the authors upon request.

Bougie Group

For patients assigned to the bougie group, operators are instructed to use a bougie on the first attempt at laryngoscopy and tracheal intubation. If the bougie is successfully placed in the trachea, an assistant is instructed to load the endotracheal tube (without a stylet) over the bougie. The operator is instructed to, without removing the laryngoscope from the mouth, advance the tube through the vocal cords to the desired depth in the trachea. If resistance is encountered when passing the endotracheal tube over the bougie, the tube is be retracted 2 centimeters, rotated 90° counterclockwise to orient the bevel tip of the tube vertically, and re-advanced into the trachea. With the operator or an assistant manually stabilizing the endotracheal tube, the bougie is withdrawn from the endotracheal tube before ventilation. Confirmation of correct endotracheal tube placement is deferred to clinicians; detection of end-tidal carbon dioxide is the standard of care at participating institutions.

This trial evaluates the use of a straight, semi-rigid bougie. Experts report that less-rigid bougies packaged in a curled position are more difficult to advance through the glottic opening.[12] Participating units use a straight bougie at least 60 cm in length; a Coudé tip is favored but not required. Operators may choose whether and how to bend the bougie prior to intubation.

Endotracheal Tube with Stylet Group

For patients assigned to the endotracheal tube with stylet group, operators are instructed to use an endotracheal tube with stylet on the first attempt at laryngoscopy and tracheal intubation. The shape and curvature of the endotracheal tube with stylet is determined the operator, however a “straight-to-cuff” shape and a distal bend angle of 25° to 35° is encouraged. If there is difficulty passing the endotracheal tube, the operator is instructed to manipulate the tube as needed, including slight retraction and rotation. The stylet remains within the endotracheal tube until the tube is within the trachea. Confirmation of correct endotracheal tube placement is deferred to clinicians; detection of end-tidal carbon dioxide is the standard of care at participating institutions.

Subsequent Attempts at Laryngoscopy and Intubation and Co-Interventions

Study group assignment determines only the device to be used on the first attempt at laryngoscopy and tracheal intubation. All other aspects of the intubation procedure are at the discretion of treating clinicians, including choice of endotracheal tube diameter, patient position, approach to pre-oxygenation, approach to ventilation and oxygenation between induction and intubation, and devices used after the first intubation attempt. For laryngoscopes capable of both video-assisted and direct laryngoscopy, the use of the video screen during intubation is at the discretion of the operator. After the first attempt at laryngoscopy and tracheal intubation, the operator may use any other method of intubation, including use of an endotracheal tube with stylet in the bougie group or use of a bougie in the endotracheal tube with stylet group. In either group, treating clinicians may, at any point, use any device they feel is required to ensure optimal care of the patient regardless of study group assignment. The approach to the

initial attempt at laryngoscopy and intubation and any co-interventions are prospectively collected and will be reported.

Co-enrollment in other randomized trials is permitted as the use of randomization facilitates balance between study arms, reduces the likelihood of any systematic effects on intubation success rates, and allows for evaluation of the main effects in this trial.

Data Collection

An observer, not directly involved with the intubation procedure, collects data for key peri-procedural outcomes, including successful intubation on the first attempt, time between induction and successful intubation, arterial oxygen saturation and systolic blood pressure at induction, and the lowest values for arterial oxygen saturation and systolic blood pressure between induction and 2 minutes following intubation. The background of trained observers depends on local context and may include either clinical professionals (e.g., physicians or nurses) or research study personnel. All observers received training on study procedures and data element definitions.

Immediately after the procedure, operators complete a paper data collection form to document the approach to oxygen administration and use of ventilation for pre-oxygenation and between induction and laryngoscopy, laryngoscope used, Cormack-Lehane grade of glottic view[13], laryngoscope video screen use (if applicable), reason for the failure to intubate on the first attempt (if applicable), subsequent intubation methods, difficult airway characteristics (cervical collar, glottic view obscured by body fluids, facial trauma), and complications of intubation (cardiac arrest, heart rate < 40 beats per minute, esophageal intubation, airway trauma, witnessed aspiration). Operators record their specialty and training level and self-report the number of prior intubations, overall and with a bougie, at the time of each study intubation.

Study personnel review the medical record to collect data on baseline characteristics, pre- and post-laryngoscopy management, and clinical outcomes. The following variables are collected:

1. Baseline: Age, gender, height, weight, race, ethnicity, APACHE II score, most recent pre-procedural Glasgow Coma Score, active medical problems at the time of intubation, active and chronic comorbidities complicating intubation, whether

the primary diagnosis was trauma-related, indication for intubation, non-invasive positive pressure ventilation and high flow nasal cannula use, vasopressor use in the hour preceding enrollment, presence of sepsis (defined as life-threatening organ dysfunction caused by a dysregulated host response to infection) or septic shock (defined as presence of sepsis plus vasopressor requirement to maintain a mean arterial pressure of 65mmHg or greater and serum lactate >2mmol/L in the absence of hypovolemia) at the time of enrollment, the highest fraction of inspired oxygen delivered (FiO_2) in the hour preceding enrollment, and whether or not this was a reintubation (defined as a patient who had been extubated from invasive mechanical ventilation within the prior 72 hours).

2. Peri-procedural: type and dose of neuromuscular blocker; laryngoscope device used, blade shape and size for first attempt; total number of intubation attempts; presence of any of the following difficult airway characteristics: vomiting, witnessed aspiration, upper gastrointestinal hemorrhage, epistaxis or oral bleeding, upper airway mass, infection, or trauma, head and neck radiation, obesity (body mass index > 30 kg/m^2), limited neck mobility, limited mouth opening, history of obstructive sleep apnea, or other.
3. 0-48 hours: Cardiac arrest within 1 hour of intubation, presence or absence of pneumothorax on first chest film obtained within 48 hours after intubation; systolic blood pressure, oxygen saturation, FiO_2, and positive end expiratory pressure delivered at 24 hours after enrollment.
4. In-Hospital Outcomes: Ventilator-free days, ICU-free days, and 28 day in-hospital mortality.

Primary Outcome

The primary outcome is successful intubation on the first attempt. Successful intubation on the first attempt is defined as placement of an endotracheal tube in the trachea following: (1) a single insertion of a laryngoscope blade into the mouth and (2) EITHER a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube into the mouth OR a single insertion of an endotracheal tube with stylet into the mouth.

The primary outcome is collected by a trained observer using a structured data collection form that records the number of insertions of the laryngoscope blade, bougie, and endotracheal tube into the patient's mouth. If data from the independent observer about the primary outcome are missing, the operator's self-report of successful intubation on the first attempt will be used. If documentation of successful intubation on the first attempt are discordant between the independent observer and the operator, data from the independent observer will take precedence.

Secondary Outcome

The secondary outcome is the incidence of severe hypoxemia, defined as an oxygen saturation less than 80% during the time interval from induction to two minutes after completion of tracheal intubation.

Exploratory Outcomes

- Cormack-Lehane grade of glottic view
- Number of laryngoscopy attempts
- Number of attempts at passing the bougie
- Number of attempts at passing the endotracheal tube
- Duration of intubation: The start of the procedure will be defined as either the time of first sedative administration or, among patients who do not receive a sedative, the time of initiation of laryngoscopy. The end of the procedure will be defined as the time of the final placement of an endotracheal tube within the trachea.
- Whether the video laryngoscope screen was viewed, among intubations where the operator used a video laryngoscope.
- Incidence of mechanical intubation complications, including:
    - Esophageal intubation
    - Operator-reported aspiration during the procedure
    - Airway trauma (injury to oropharyngeal, glottic, or thoracic airway structures)
- Cardiac arrest within 1 hour following intubation

- Incidence of peri-intubation cardiovascular collapse, defined as one or more of:
    - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation
    - New or increased vasopressor between induction and 2 minutes following intubation
    - Cardiac arrest within 1 hour of intubation
    - Death within 1 hour of intubation
- ICU-free days in the first 28 days (see Supplementary file, section 3)
- Ventilator free days in the first 28 days (see Supplementary file, section 2)
- All-cause, in-hospital mortality at 28 days

Sample Size Estimation

There is no established minimum clinically important difference in successful intubation on the first attempt. A prior single-center randomized trial reported an absolute difference of 11% in successful intubation on the first attempt between the bougie and endotracheal tube with stylet groups. Because this trial was performed in an ED where the majority of first intubation attempts utilized a bougie, we anticipated a potentially smaller difference between groups in this multicenter trial conducted in a broader range of clinical settings with a broader range of operators. Therefore, the current trial was designed to detect a 6% absolute difference between groups in the proportion of patients who experience successful intubation on the first attempt. For two inexpensive interventions already routinely available and utilized in practice, the minimally clinically significant difference that would be expected to change practice is unknown. However, an absolute difference of 6% in successful intubation on the first attempt is similar to or smaller than the difference considered to be clinically meaningful in the design of prior airway management trials.[7,10,14] Assuming 84% of patients in the endotracheal tube with stylet group experience successful intubation on the first laryngoscopy attempt, detecting a 6% absolute increase in successful intubation on the first attempt with 80% power at a two-sided alpha level of 0.05 would require enrollment of 1,050 patients (525 per group). Anticipating missing data for 5% of patients or less, we will plan to enroll a total of 1,106 patients (553 per group).

Data and Safety Monitoring Board (DSMB) and Interim Analysis

A DSMB composed of 4 clinical trials experts with backgrounds in critical care medicine, anesthesia, and emergency medicine has overseen the design of the trial and is monitoring its conduct. The DSMB reviewed a single interim analysis, prepared by the study biostatistician, on February 4th, 2020, at the anticipated halfway point of the trial after enrollment of 553 patients, and recommended continuing the trial to completion without alteration. The stopping boundary for efficacy was pre-specified as a P-value of 0.001 or less for the difference in the incidence of the primary outcome between groups tested, using a chi-square test. This conservative Haybittle–Peto boundary was selected to allow the final analysis to be performed using an unchanged level of significance ($P < 0.05$). The recommended stopping boundary for safety was a $P < 0.025$ comparing the incidence of esophageal intubation and separately the incidence of airway trauma between groups, using a chi-square test. The DSMB retains the authority to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol to protect patient safety.

Statistical Analysis Principles

Analyses will be conducted following reproducible research principles using R (R Foundation for Statistical Computing, Vienna, Austria).[15] Continuous variables will be reported as mean ± standard deviation or median and interquartile range; categorical variables will be reported as frequencies and proportions. Between-group comparisons will be made with the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. We will also present absolute between-group differences with associated 95% confidence intervals. A two-sided p-value of < 0.05 will be used to indicate statistical significance; with just one primary outcome, no adjustment for multiplicity will be made. For secondary and exploratory analyses, emphasis will be placed on the magnitude of differences between groups rather than statistical significance.

Main Analysis of the Primary Outcome

The main analysis will be an unadjusted, intention-to-treat comparison of successful intubation on the first attempt between patients randomized to the bougie group and patients randomized to the endotracheal tube with stylet group, using a chi-square test.

Secondary Analyses of the Primary Outcome

Multivariable modeling to account for covariates

To account for relevant covariates, we will develop a generalized linear mixed effects model using a logit link function with the primary outcome as the dependent variable, study site and operator as random effects, and fixed effects of study group and the following pre-specified baseline covariates: age, sex, race, body-mass index, operator experience quantified as the operator's total number of prior intubations, and location of intubation (ED vs ICU). We will then construct a model with the following additional factors that may be interpreted as baseline covariates but which are unable to be assessed until after randomization: use of a video vs direct laryngoscope; presence of ≥ 1 difficult airway characteristic (obesity, body fluids obscuring glottic view, cervical immobilization, or facial trauma) and Cormack-Lehane grade 2, 3, or 4 laryngeal view. All continuous variables will be modeled assuming a nonlinear relationship to the outcome using restricted cubic splines with between 3 and 5 knots.

Effect Modification

We will examine whether pre-specified variables modify the effect of bougie vs endotracheal tube with stylet use on the primary outcome using a formal test of interaction between group assignment and effect modifier in the above models. Because this study is not formally designed or powered to test for interaction, a less conservative P value for the interaction term will be used, with values less than 0.10 considered suggestive of a potential interaction and values less than 0.05 considered to confirm an interaction. We will examine whether the following baseline variables modify the effect of study group on the primary outcome:

1. Operator Experience at the time of each enrollment
    a. Total number of previous intubations performed by operator

    b. Number of previous intubations performed by operator using a bougie
    c. Proportion of previous intubations performed by the operator that were performed using a bougie
2. Location (ED vs ICU)
3. Indication for intubation (trauma vs medical)
4. Difficult airway, defined as one or more of the following difficult airway characteristics: obesity (body mass index > 40 kg/m^2), cervical immobilization, or facial trauma.
5. Time period (before the COVID pandemic vs during or after the COVID pandemic)

In addition to the variables above, which can be assessed prior to enrollment, we will perform exploratory analyses examining additional potential effect modifiers that are intended to represent baseline variables, but which are collected after enrollment, and therefore have the potential to be affected by study group assignment. These include:

1. Laryngoscope type (Direct laryngoscope [without video capability] vs video laryngoscope [with video capability])
2. Presence body fluids obscuring glottic view (Yes vs No)
3. Cormack Lehane grade of view (1 vs 2-4).

Sensitivity Analyses of the Primary Outcome

To assess the robustness of the findings, we will repeat the main analysis of the primary outcome in several alternatives to the overall intention-to-treat population. First, we will repeat the main analysis of the primary outcome among only those patients for whom a non-hyperangulated laryngoscope blade was used on the first attempt at intubation. Second, operators may choose to deviate from the assigned device for the safety of the patient after obtaining a laryngeal view. To address this, we will repeat the main analysis of the primary outcome for all patients, but will assign failure to the first intubation attempt for patients in whom the operator crossed over from the assigned device to the non-assigned device. Third, we will repeat the main analysis of the primary outcome, including only cases in which primary outcome data from the independent

observer is complete (i.e., excluding cases in which the operator's self-report of whether there was successful intubation on the first attempt defined the primary outcome for that patient). Fourth, because prior intubating experience may influence success with both devices, we will repeat the main analysis of the primary outcome, excluding cases where the operator had ≤ 10 total prior intubations. Fifth, because prior experience with using a bougie may influence successful intubation in the bougie group, we will repeat the main analysis of the primary outcome, excluding cases where the operator had ≤ 5 prior intubations while using a bougie. Sixth, we will perform a sensitivity analysis that defines successful intubation on the first attempt as successful tracheal intubation during the first insertion of the laryngoscope blade, regardless of the number of insertions of a bougie or endotracheal tube.

Analysis of the Secondary Outcome

For the secondary outcome, severe hypoxemia (lowest oxygen saturation < 80%), we will perform an unadjusted, intention-to-treat comparison of patients randomized to the bougie group versus patients randomized to the endotracheal tube with stylet group, using a chi-square test.

Analyses of Exploratory Outcomes

For all pre-specified exploratory outcomes, we will conduct unadjusted, intention-to-treat analyses comparing patients randomized to the bougie to patients randomized to the endotracheal tube with stylet. Continuous outcomes will be compared with the Wilcoxon rank sum test and categorical variables with a chi-square test. Between-group differences in continuous and categorical variables and the associated 95% confidence intervals will be presented.

Handling of Missing Data

We anticipate that no data on the primary outcome will be missing. When data are missing for the secondary or exploratory outcomes, we will perform complete-case analysis, excluding cases where the data for the analyzed outcome are missing. There

will be no imputation of missing data for these outcomes. In adjusted analyses, missing data for covariates will be imputed using multiple imputations.

Trial status

The BOugie or Stylet In Patients UnderGoing Intubation Emergently (BOUGIE) trial is a pragmatic, prospective, multi-center, non-blinded randomized clinical trial comparing use of a bougie to use of an endotracheal tube with stylet for tracheal intubation of critically ill adults in the ED and ICU. Patient enrollment began on 29 April 2019.

Pause in Enrollment

Over the first 10 months of enrollment, four patients were enrolled and subsequently found to be prisoners. On February 28, 2020, we paused enrollment to evaluate and improve enrollment procedures with a goal of preventing the enrollment of ineligible patients. The decision was made to extend the pause in enrollment during the early stages of the COVID-19 pandemic when enrollment was felt to be infeasible. Enrollment was resumed on August 24, 2020 with introduction of a new pre-procedural "time out" which requires the verbal recitation of eligibility criteria prior to enrollment to prevent subsequent enrollments of ineligible patients.

Ethics and Dissemination

Waiver of Informed Consent

Critically ill patients undergoing tracheal intubation in the ED or ICU are at significant risk for morbidity and mortality from their underlying illness. Most patients undergoing tracheal intubation in routine clinical care receive intubation using either a bougie or an endotracheal tube with stylet on the first attempt. Any benefits or risks of these two approaches are experienced by patients undergoing tracheal intubation in clinical care, outside the context of research. As a requirement for enrollment in the BOUGIE trial, the patient's treating clinician must believe that either a bougie or an endotracheal tube with stylet would be a safe and reasonable approach for the patient (otherwise the patient is excluded). Therefore, making the decision between the two approaches randomly (by study group assignment) rather than by a provider who thinks either approach is safe

and reasonable for the patient was expected to pose no more than minimal additional risk.

The investigators also determined that obtaining informed consent for participation in the study would be impracticable. Tracheal intubation of acutely ill patients is a time-sensitive procedure. Despite the availability of an informed consent document for the intubation procedure in clinical care, the risks and benefits of the procedure are infrequently discussed and the informed consent document for the procedure in clinical care is infrequently completed before the procedure due to its time-sensitive nature, the impairments induced by the patients' critical illness, and the frequent absence of surrogate decision makers.

Because the study was expected to pose minimal risk and prospective informed consent was considered to be impracticable, a waiver of informed consent was requested and granted from all institutional review boards overseeing the trial. This is consistent with previous randomized trials comparing alternative approaches to tracheal intubation commonly used in clinical care.[7,10,16–21]

Information for Patients and Families

Information regarding the study is made available to patients and families by at least one of the following mechanisms, with the choice between the mechanisms determined by the local context assessment of the site IRB and site principal investigators: (1) a patient and family notification sheet provided to each patient and family following enrollment, informing the patient of their enrollment and describing the study; (2) a patient and family information sheet posted in at least three publicly-visible locations within the study unit containing general information about the study and contact information for the research team for additional questions or concerns; or (3) a patient and family information sheet provided to each patient and family on admission as part of an "admission packet" containing general study information and contact information for the research team for additional questions or concerns.

Protocol Changes

Any further amendments to the protocol will be recorded on ClinicalTrials.Gov as per SPIRIT guidelines. See Supplemental file, section 5 for more details on how protocol changes will be handled.

Dissemination Plan

Trial results will be submitted to a peer-reviewed journal and will be presented at one or more scientific conferences.

Conclusion

In the interest of allowing for a clearer and more objective interpretation of the trial results, this description of the trial protocol delineates the BOUGIE trial methods and analysis prior to the conclusion of enrollment.

	STUDY PERIOD						
	Eligibility Screen	**Randomize & Allocate**	**Peri-Procedural**				**Final Outcome Assessment**
TIMEPOINT	***Decision to perform TI***	**Prior to TI**	***Induction***	***TI***	***0-2 min post-TI***	**0-48 hrs post-TI**	***Discharge or 30 days after enrollment***
ENROLLMENT:		X					
Eligibility screen	X						
Allocation		X					
INTERVENTIONS:							
Bougie				X			
Endotracheal tube with stylet				X			
Screening for contraindications	X	X	X	X			
ASSESSMENTS:							
Baseline Variables	X	X					
Peri-procedural variables		X	X	X	X		
Clinical Outcomes						X	X

Figure 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, interventions, and assessments. TI, Tracheal Intubation; Induction, administration of a sedative or neuromuscular blocking agent

List of BOUGIE Investigators

Vanderbilt University Medical Center— Matthew W. Semler, MD, MSc***; Wesley H. Self, MD, MPH***; Christopher G Hughes, MD, MS***; Janna S. Landsperger, MSN***; Li Wang, MS***; Christopher J. Lindsell PhD***; Todd W. Rice, MD, MSc***; Jonathan D. Casey, MD, MSc***; Christopher S. Gray, RN**; Kevin High, RN, MPH**; Andrea Fletcher, RN**; Sally Dye, RN**; Bradley Lloyd, RRT-ACCS*; Bret D. Alvis, MD*.
University of Colorado School of Medicine— Adit A Ginde, MD, MPH***; Michelle P Howell, RN, BSN***; Robert Mitchell, RRT**; Justin Oeth, RN, MSN**; Anthony Defebio*; Jennifer Friedel*; Feysel Mohamed*; Karina Nava*; Angela Otoo*; Christian Perez*; Cori Withers*.
University of Alabama at Birmingham Medical Center— Sheetal Gandotra, MD***; David B Page, MD***; Micah R Whitson, MD***; Derek W. Russell, MD***; Swati Gulati, MBBS, MS***; Sarah W. Robison, MD**; Michael C. Kurz, MD, MS**; Anna Altz-Stamm RN, BSN, CCRN*; Cristina Bardita, MD, PhD*; Mary Clay Boone RN, BSN*; Joe W. Chiles III, MD*; Kristina Collins RN, BSN*; Abby Drescher RN, BSN*; Kevin G. Dsouza, MD*; Janna Dunn, RN, ADN*; Stacy Ejem, MD*; Josh Gautney, MD*; Nicole Harris, RN, ADN*; Savannah Herder, RN, BSN*; Tamer Hudali, MD, MPH*; R. Chad Wade, MD*; Rutwij Joshi, MBBS*; Daniel Kelmenson, MD*; Anne Merrill Mason RN, BSN*; Scott R. Merriman, MD*; Takudzwa Mkorombindo, MD*; Megan Moore, RN, MSN*; Jada Nowak, RN, BSN*; Kate O'Connor, DO*; Sheylan D. Patel, MD*; G. Bruno Pereira, MD, PhD*; Lisa Sarratt RN, BSN*; Tabitha Stewart RN, BSN*; William S. Stigler, MD*; Kadambari Vijaykumar, MBBS*; Gina White RN, BSN*; Stephanie C. Demasi, MD*; Laura E. Goyack, MD*.
Denver Health Medical Center— Stacy A Trent, MD, MPH***; Carol L. Lyle, MPH, PA-C**; Alicia K. Cupelo, MSW**.
Wake Forest School of Medicine— Lane M Smith, MD, PhD***; John P Gaillard, MD***; Kevin W. Gibbs, MD***; Erika L.W. Rice, DO**; Nathaniel D. Westphal, MD**; Kristy K. Ford, MD*; Trevor S. Mattox, MD*.
Ochsner Health System New Orleans— Derek J Vonderhaar, MD***.
University of Washington Harborview Medical Center— Aaron M. Joffe, DO***; Itay Bentov, MD, PhD***; Steven H Mitchell, MD***; Andrew J Latimer, MD***; Christopher Barnes**; Andrew M. Walters**; Tak Watase, MD MBA*.
Lincoln Medical Center— Jason R West, MD***.
University of Iowa Hospitals and Clinics— Kevin Doerschug, MD***; Vikas Koppurapu, MD**.
Duke University School of Medicine— Vijay Krishnamoorthy, MD, PhD*; Raquel R Bartz, MD*; William C Fox, MD*; John Whittle, MBBS, MD*.
Louisiana State University School of Medicine—David R Janz, MD, MSc***.
Hennepin County Medical Center— Brian E Driver, MD***; Matthew E Prekker, MD MPH***; Jamie Stang, BS**; Paige DeVries, BS**; Alexandra Schick, MD**.

***Denotes an author listed on the byline.
**Denotes an author not listed on the byline due to space considerations.
*Denotes a collaborator

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BOugie or stylet in patients UnderGoing Intubation Emergently (BOUGIE): protocol and statistical analysis plan for a randomised clinical trial

Brian Driver ,[1] Matthew W Semler ,[2] Wesley H Self,[3] Adit A Ginde,[4] Sheetal Gandotra ,[5,6] Stacy A Trent,[4,7] Lane M Smith,[8] John P Gaillard,[8] David B Page,[9,10] Micah R Whitson,[9,10] Derek J Vonderhaar,[11] AM Joffe,[12] Jason R West ,[13] Christopher Hughes,[14] Janna S Landsperger,[2] Michelle P Howell,[4] Derek W Russell ,[5,6] Swati Gulati,[5,6] Itay Bentov,[12] Steven Mitchell,[15] Andrew Latimer,[15] Kevin Doerschug,[16] Vikas Koppurapu,[16] Kevin W Gibbs,[17] Li Wang,[18] Christopher John Lindsell,[18] David Janz,[19] Todd W Rice,[2] Matthew E Prekker,[1,20] Jonathan D Casey,[2] BOUGIE Investigators# and the Pragmatic Critical Care Research Group

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BD and MWS contributed equally.
MEP and JDC contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Brian Driver;
briandriver@gmail.com

ABSTRACT

Introduction Intubation-related complications are less frequent when intubation is successful on the first attempt. The rate of first attempt success in the emergency department (ED) and intensive care unit (ICU) is typically less than 90%. The bougie, a semirigid introducer that can be placed into the trachea to facilitate a Seldinger-like technique of tracheal intubation and is typically reserved for difficult or failed intubations, might improve first attempt success. Evidence supporting its use, however, is from a single academic ED with frequent bougie use. Validation of these findings is needed before widespread implementation.

Methods and analysis The BOugie or stylet in patients Undergoing Intubation Emergently trial is a prospective, multicentre, non-blinded randomised trial being conducted in six EDs and six ICUs in the USA. The trial plans to enrol 1106 critically ill adults undergoing orotracheal intubation. Eligible patients are randomised 1:1 for the use of a bougie or use of an endotracheal tube with stylet for the first intubation attempt. The primary outcome is successful intubation on the first attempt. The secondary outcome is severe hypoxaemia, defined as an oxygen saturation less than 80% between induction until 2 min after completion of intubation. Enrolment began on 29 April 2019 and is expected to be completed in 2021.

Ethics and dissemination The trial protocol was approved with waiver of informed consent by the Central Institutional Review Board at Vanderbilt University Medical Center or the local institutional review board at an enrolling site. The results will be submitted for publication in a peer-reviewed journal and presented at scientific conferences.

Trial registration number ClinicalTrials.gov Registry (NCT03928925).

Strengths and limitations of this study

- ► This protocol provides a detailed description of the largest pragmatic trial of bougie use in emergency airway management to be conducted to date.
- ► Broad eligibility criteria, diverse prior experience with a bougie among operators and conduct in the emergency department and intensive care unit at multiple centres will increase the external validity of the findings.
- ► Patients, clinicians and investigators are not blinded to study group assignment after randomisation.

INTRODUCTION

Tracheal intubation of critically ill adults is frequently performed in the emergency department (ED) and intensive care unit (ICU). Successful intubation on the first attempt has been associated with a lower incidence of peri-intubation complications.[1–4] However, less than 90% of patients are intubated on the first attempt in most settings outside of the operating room, highlighting an opportunity for improvement.[5–7]

Emergency tracheal intubation is commonly performed in three discrete steps. First, medications are administered to facilitate optimal intubating conditions (induction). Second, a laryngoscope is inserted into the patient's mouth and a direct or indirect video view of glottic structures is obtained (laryngoscopy). Third, an endotracheal tube is placed in the mouth and advanced past the vocal cords into the trachea (intubation). Two commonly used devices that aid in placing the endotracheal tube include: a stylet (a malleable, metal rod preloaded inside the endotracheal tube

to facilitate navigation of the upper airway) or a bougie (a thin, plastic introducer passed into the trachea which serves as a guide for passage of the endotracheal tube). When using a stylet, the endotracheal tube and stylet are passed into the trachea together. When using a bougie, the bougie is first passed into the trachea and then the endotracheal tube is advanced over the bougie using a Seldinger-like technique. There is substantial variation between clinicians as to whether they select the stylet or the bougie for the first intubation attempt.[5 8] For some physicians, the bougie is used primarily as a rescue device in the event difficulty is encountered in laryngoscopy or passage of the endotracheal tube with stylet. Other physicians use a bougie routinely on the first attempt at tracheal intubation.[8 9]

To our knowledge, only one prior randomised trial has compared rates of successful intubation on the first attempt outside of the operating room with use of a bougie versus use of endotracheal tube with stylet: the single-centre Bougie Use in Emergency Airway Management (BEAM) trial. That study showed a higher rate of successful intubation on the first attempt with use of a bougie (98%) compared with use of an endotracheal tube with stylet (87%) in adult ED patients (absolute difference 11%, 95% CI 7% to 14%).[10] However, it is possible that these findings reflect increased institution-specific comfort with bougie use compared with the endotracheal tube and stylet—operators reported using a bougie in approximately 80% of intubations before the trial.[8] It is unknown if the results of the BEAM trial will generalise to other settings where operators have less experience using the bougie and have greater experience using an endotracheal tube with stylet during the first attempt at intubation.

METHODS AND ANALYSIS

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see table 1 and online supplemental file 1, section 1).[11]

Patient and public involvement

We did not involve patients or the public in the design of the study.

Study design

The BOugie or stylet in patients UnderGoing Intubation Emergently (BOUGIE) trial is a pragmatic, multicenter, unblinded, parallel-group, randomised trial comparing use of a bougie to use of an endotracheal tube with stylet for the first attempt at tracheal intubation among critically ill adults in the ED and ICU. The primary outcome is successful intubation on the first attempt. An independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial. Study sites and investigators are listed in online supplemental file 1, sections 2 and 3.

Study population

The inclusion criteria for the trial are:

1. Patient is located in a participating unit of an adult hospital.
2. Planned procedure is tracheal intubation with sedative administration (or tracheal intubation without sedative administration in patients with decreased level of consciousness, cardiac arrest or respiratory arrest).
3. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit.
4. Planned laryngoscopy device is a non-hyperangulated laryngoscope blade.

The exclusion criteria for the trial are:

1. Patient is pregnant.
2. Patient is a prisoner.
3. Urgency of intubation precludes safe performance of study procedures.
4. Operator feels an approach to intubation other than use of a bougie or use of an endotracheal tube with stylet would be best for the care of the patient.
5. Operator feels use of a bougie is required or contraindicated for the care of the patient.
6. Operator feels use of an endotracheal tube with stylet is required or contraindicated for the care of the patient.

The original inclusion criteria specified that patients must be at least 18 years old to be eligible. With approval from the Central Institutional Review Board at Vanderbilt University Medical Center, trial inclusion and exclusion criteria were amended on 16 January 2020 to allow the enrolment of patients less than 18 years of age. Because the identity and age of critically ill patients presenting to the ED are sometimes unknown (eg, a patient with cardiac arrest presenting by ambulance without family), this criterion was revised to include patients located in a participating unit of an adult hospital. We anticipate that a small number of patients whose identity and age are unknown, who are judged by treating clinicians to be an adult and enrolled in the trial, will later be determined to be less than 18 years old.

Randomisation and treatment allocation

Patients are randomised in a 1:1 ratio to undergo intubation using a bougie or using an endotracheal tube with stylet for the first attempt in permuted blocks of two, four or six, stratified by study site. Study-group assignments are generated using a computerised randomisation sequence, placed in sequentially numbered opaque envelopes and distributed to enrolling sites. Before opening the envelope, the operator determines that the patient meets all inclusion criteria and no exclusion criteria. The operator documents whether they plan to use a video laryngoscope or a direct laryngoscope by checking a box on the front of the envelope. The operator then opens the envelope. Patients are considered to be enrolled once the operator opens the envelope to reveal study group assignment. Thus, group assignment is concealed until after documentation of laryngoscope choice and patient

Table 1 Standard Protocol Items: Recommendations for Interventional Trials checklist, enrolment, interventions and assessments.

Study period						
	Eligibility screen	Randomise and allocate	Periprocedural			Final outcome assessment
Timepoint	**Decision to perform TI**	**Before TI**	**Induction**	**TI**	**0–2 min post TI**	**0–48 hours post TI**	**Discharge or 30 days after enrolment**
Enrolment:		X					
Eligibility screen	X						
Allocation		X					
Interventions:							
Bougie				X			
Endotracheal tube with stylet				X			
Screening for contraindications	X	X	X	X			
Assessments:							
Baseline variables	X	X					
Periprocedural variables		X	X	X	X		
Clinical outcomes						X	X

Induction, Administration of a sedative or neuromuscular blocking agent; TI, tracheal intubation.

enrolment. Patients who are screened and excluded will be reported with trial results using a Consolidated Standards of Reporting Trials diagram. After enrolment and randomisation, patients, treating clinicians and study personnel are not blinded to study group assignment.

Study interventions

Training

Before beginning enrolment at a site, operators at each site received a 30 min in-person lecture and watched a 6 min training video which demonstrated best practices for intubation with both a bougie and endotracheal tube with stylet. These materials are available from the authors on request.

Bougie group

For patients assigned to the bougie group, operators are instructed to use a bougie on the first attempt at laryngoscopy and tracheal intubation. If the bougie is successfully placed in the trachea, an assistant is instructed to load the endotracheal tube (without a stylet) over the bougie. The operator is instructed to, without removing the laryngoscope from the mouth, advance the tube through the vocal cords to the desired depth in the trachea. If resistance is encountered when passing the endotracheal tube over the bougie, the tube is be retracted 2 cm, rotated 90° counterclockwise to orient the bevel tip of the tube vertically and readvanced into the trachea. With the operator or an assistant manually stabilising the endotracheal tube, the bougie is withdrawn from the endotracheal tube before ventilation. Confirmation of correct endotracheal tube placement is deferred to clinicians; detection of end-tidal carbon dioxide is the standard of care at participating institutions.

This trial evaluates the use of a straight, semirigid bougie. Experts report that less-rigid bougies packaged in a curled position are more difficult to advance through the glottic opening.[12] Participating units use a straight bougie at least 60 cm in length; a coudé tip is favoured but not required. Operators may choose whether and how to bend the bougie prior to intubation.

Endotracheal tube with stylet group

For patients assigned to the endotracheal tube with stylet group, operators are instructed to use an endotracheal tube with stylet on the first attempt at laryngoscopy and tracheal intubation. The shape and curvature of the endotracheal tube with stylet is determined by the operator, however a 'straight-to-cuff' shape and a distal bend angle of 25°–35° is encouraged. If there is difficulty passing the endotracheal tube, the operator is instructed to manipulate the tube as needed, including slight retraction and rotation. The stylet remains within the endotracheal tube until the tube is within the trachea. Confirmation of correct endotracheal tube placement is deferred to clinicians; detection of end-tidal carbon dioxide is the standard of care at participating institutions.

Subsequent attempts at laryngoscopy and intubation and cointerventions

Study group assignment determines only the device to be used on the first attempt at laryngoscopy and tracheal intubation. All other aspects of the intubation procedure are at the discretion of treating clinicians, including choice of endotracheal tube diameter, patient position, approach to preoxygenation, approach to ventilation and oxygenation between induction and intubation and devices used after the first intubation attempt. For laryngoscopes capable of both video-assisted and direct laryngoscopy, the use of the video screen during intubation is at the discretion of the operator. After the first attempt at laryngoscopy and tracheal intubation, the operator may use any other method of intubation, including use of an endotracheal tube with stylet in the bougie group or use of a bougie in the endotracheal tube with stylet group. In either group, treating clinicians may, at any point, use any device they feel is required to ensure optimal care of the patient regardless of study group assignment. The approach to the initial attempt at laryngoscopy and intubation and any cointerventions are prospectively collected and will be reported.

Coenrolment in other randomised trials is permitted as the use of randomisation facilitates balance between study arms, reduces the likelihood of any systematic effects on intubation success rates and allows for evaluation of the main effects in this trial.

Data collection

An observer, not directly involved with the intubation procedure, collects data for key periprocedural outcomes, including successful intubation on the first attempt, time between induction and successful intubation, arterial oxygen saturation and systolic blood pressure at induction and the lowest values for arterial oxygen saturation and systolic blood pressure between induction and 2 min following intubation. The background of trained observers depends on local context and may include either clinical professionals (eg, physicians or nurses) or research study personnel. All observers received training on study procedures and data element definitions.

Immediately after the procedure, operators complete a paper data collection form to document the approach to oxygen administration and use of ventilation for preoxygenation and between induction and laryngoscopy, laryngoscope used, Cormack-Lehane grade of glottic view[13], laryngoscope video screen use (if applicable), reason for the failure to intubate on the first attempt (if applicable), subsequent intubation methods, difficult airway characteristics (cervical collar, glottic view obscured by body fluids, facial trauma) and complications of intubation (cardiac arrest, heart rate <40 beats per minute, oesophageal intubation, airway trauma, witnessed aspiration). Operators record their specialty and training level and self-report the number of prior intubations, overall and with a bougie, at the time of each study intubation.

Study personnel review the medical record to collect data on baseline characteristics, pre and post laryngoscopy management and clinical outcomes. The following variables are collected:

1. Baseline: Age, gender, height, weight, race, ethnicity, APACHE (acute physiology and chronic health evaluation) II Score, most recent preprocedural Glasgow Coma Score, active medical problems at the time of intubation, active and chronic comorbidities complicating intubation, whether the primary diagnosis was trauma related, indication for intubation, non-invasive positive pressure ventilation and high flow nasal cannula use, vasopressor use in the hour preceding enrolment, presence of sepsis (defined as life-threatening organ dysfunction caused by a dysregulated host response to infection) or septic shock (defined as presence of sepsis plus vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate >2 mmol/L in the absence of hypovolemia) at the time of enrolment, the highest fraction of inspired oxygen delivered (FiO_2) in the hour preceding enrolment and whether or not this was a reintubation (defined as a patient who had been extubated from invasive mechanical ventilation within the prior 72 hours).
2. Periprocedural: Type and dose of neuromuscular blocker; laryngoscope device used, blade shape and size for first attempt; total number of intubation attempts and presence of any of the following difficult airway characteristics: vomiting, witnessed aspiration, upper gastrointestinal haemorrhage, epistaxis or oral bleeding, upper airway mass, infection or trauma, head and neck radiation, obesity (body mass index >30 kg/m^2), limited neck mobility, limited mouth opening, history of obstructive sleep apnea or other.
3. 0–48 hours: Cardiac arrest within 1 hour of intubation, presence or absence of pneumothorax on first chest film obtained within 48 hours after intubation and systolic blood pressure, oxygen saturation, FiO_2 and positive end expiratory pressure delivered at 24 hours after enrolment.
4. In-hospital outcomes: Ventilator-free days, ICU-free days and 28 days in-hospital mortality.

Primary outcome

The primary outcome is successful intubation on the first attempt. Successful intubation on the first attempt is defined as placement of an endotracheal tube in the trachea following: (1) a single insertion of a laryngoscope blade into the mouth and (2) either a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube into the mouth or a single insertion of an endotracheal tube with stylet into the mouth.

The primary outcome is collected by a trained observer using a structured data collection form that records the number of insertions of the laryngoscope blade, bougie and endotracheal tube into the patient's mouth. If data from the independent observer about the primary outcome are missing, the operator's self-report of successful intubation on the first attempt will be used. If documentation of successful intubation on the first attempt is discordant between the independent observer and the operator, data from the independent observer will take precedence.

Secondary outcome

The secondary outcome is the incidence of severe hypoxaemia, defined as an oxygen saturation less than 80% during the time interval from induction to 2 min after completion of tracheal intubation.

Exploratory outcomes

- Cormack-Lehane grade of glottic view.
- Number of laryngoscopy attempts.
- Number of attempts at passing the bougie.
- Number of attempts at passing the endotracheal tube.
- Duration of intubation: The start of the procedure will be defined as either the time of first sedative administration or, among patients who do not receive a sedative, the time of initiation of laryngoscopy. The end of the procedure will be defined as the time of the final placement of an endotracheal tube within the trachea.
- Whether the video laryngoscope screen was viewed, among intubations where the operator used a video laryngoscope.
- Incidence of mechanical intubation complications, including:
  Oesophageal intubation.
  Operator-reported aspiration during the procedure.
  Airway trauma (injury to oropharyngeal, glottic or thoracic airway structures).
- Cardiac arrest within 1 hour following intubation.
- Incidence of peri-intubation cardiovascular collapse, defined as one or more of:
  New systolic blood pressure<65 mm Hg between induction and 2 min following intubation.
  New or increased vasopressor between induction and 2 min following intubation.
  Cardiac arrest within 1 hour of intubation.
  Death within 1 hour of intubation.
- ICU-free days in the first 28 days (see online supplemental file 1, section 4).
- Ventilator-free days in the first 28 days (see online supplemental file 1, section 5).
- All-cause, in-hospital mortality at 28 days.

Sample size estimation

There is no established minimum clinically important difference in successful intubation on the first attempt. A prior single-centre randomised trial reported an absolute difference of 11% in successful intubation on the first attempt between the bougie and endotracheal tube with stylet groups. Because this trial was performed in an ED where the majority of first intubation attempts used a bougie, we anticipated a potentially smaller difference

between groups in this multicenter trial conducted in a broader range of clinical settings with a broader range of operators. Therefore, the current trial was designed to detect a 6% absolute difference between groups in the proportion of patients who experience successful intubation on the first attempt. For two inexpensive interventions already routinely available and used in practice, the minimally clinically significant difference that would be expected to change practice is unknown. However, an absolute difference of 6% in successful intubation on the first attempt is similar to or smaller than the difference considered to be clinically meaningful in the design of prior airway management trials.[7 10 14] Assuming 84% of patients in the endotracheal tube with stylet group experience successful intubation on the first laryngoscopy attempt, detecting a 6% absolute increase in successful intubation on the first attempt with 80% power at a two-sided alpha level of 0.05 would require enrolment of 1050 patients (525 per group). Anticipating missing data for 5% of patients or less, we will plan to enrol a total of 1106 patients (553 per group).

DSMB and interim analysis

A DSMB composed of four clinical trials experts with backgrounds in critical care medicine, anaesthesia and emergency medicine has overseen the design of the trial and is monitoring its conduct. The DSMB reviewed a single interim analysis, prepared by the study biostatistician, on 4 February 2020, at the anticipated halfway point of the trial after enrolment of 553 patients, and recommended continuing the trial to completion without alteration. The stopping boundary for efficacy was prespecified as a p value of 0.001 or less for the difference in the incidence of the primary outcome between groups tested, using a χ^2 test. This conservative Haybittle-Peto boundary was selected to allow the final analysis to be performed using an unchanged level of significance ($p<0.05$). The recommended stopping boundary for safety was a $p<0.025$ comparing the incidence of oesophageal intubation and separately the incidence of airway trauma between groups, using a χ^2 test. The DSMB retains the authority to stop the trial at any point, request additional data or interim analyses or request modifications of the study protocol to protect patient safety. The DSMB charter is available in online supplemental file 1, section 6. Patient privacy and data storage details are listed in online supplemental file 1, section 7.

Statistical analysis principles

Analyses will be conducted following reproducible research principles using R (R Foundation for Statistical Computing, Vienna, Austria).[15] Continuous variables will be reported as mean±SD deviation or median and IQR; categorical variables will be reported as frequencies and proportions. Between-group comparisons will be made with the Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. We will also present absolute between-group differences with associated 95% CIs. A two-sided p value of <0.05 will be used to indicate statistical significance; with just one primary outcome, no adjustment for multiplicity will be made. For secondary and exploratory analyses, emphasis will be placed on the magnitude of differences between groups rather than statistical significance.

Main analysis of the primary outcome

The main analysis will be an unadjusted, intention-to-treat comparison of successful intubation on the first attempt between patients randomised to the bougie group and patients randomised to the endotracheal tube with stylet group, using a χ^2 test.

Secondary analyses of the primary outcome

Multivariable modeling to account for covariates

To account for relevant covariates, we will develop a generalised linear mixed effects model using a logit link function with the primary outcome as the dependent variable, study site and operator as random effects and fixed effects of study group and the following prespecified baseline covariates: age, sex, race, body mass index, operator experience quantified as the operator's total number of prior intubations and location of intubation (ED vs ICU). We will then construct a model with the following additional factors that may be interpreted as baseline covariates but which are unable to be assessed until after randomisation: use of a video versus direct laryngoscope; presence of ≥1 difficult airway characteristic (obesity, body fluids obscuring glottic view, cervical immobilisation or facial trauma) and Cormack-Lehane grade 1 vs grade 2, 3 or 4 laryngeal view. All continuous variables will be modelled assuming a non-linear relationship to the outcome using restricted cubic splines with between 3 and 5 knots.

Effect modification

We will examine whether prespecified variables modify the effect of bougie versus endotracheal tube with stylet use on the primary outcome using a formal test of interaction between group assignment and effect modifier in the above models. Because this study is not formally designed or powered to test for interaction, a less conservative p value for the interaction term will be used, with values less than 0.10 considered suggestive of a potential interaction and values less than 0.05 considered to confirm an interaction. We will examine whether the following baseline variables modify the effect of study group on the primary outcome:

1. Operator experience at the time of each enrolment.
   a. Total number of previous intubations performed by operator.
   b. Number of previous intubations performed by operator using a bougie.
   c. Proportion of previous intubations performed by the operator that were performed using a bougie.
2. Location (ED vs ICU).
3. Indication for intubation (trauma vs medical).

4. Difficult airway, defined as one or more of the following difficult airway characteristics: obesity (body mass index>30 kg/m^2), cervical immobilisation or facial trauma.
5. Time period (before the COVID-19 pandemic vs during or after the COVID-19 pandemic).

In addition to the variables above, which can be assessed prior to enrolment, we will perform exploratory analyses examining additional potential effect modifiers that are intended to represent baseline variables, but which are collected after enrolment, and therefore have the potential to be affected by study group assignment. These include:

1. Laryngoscope type (direct laryngoscope (without video capability) vs video laryngoscope (with video capability)).
2. Presence body fluids obscuring glottic view (yes vs no).
3. Cormack-Lehane grade of view (1 vs 2–4).

Sensitivity analyses of the primary outcome

To assess the robustness of the findings, we will repeat the main analysis of the primary outcome in several alternatives to the overall intention-to-treat population. First, we will repeat the main analysis of the primary outcome among only those patients for whom a non-hyperangulated laryngoscope blade was used on the first attempt at intubation. Second, operators may choose to deviate from the assigned device for the safety of the patient after obtaining a laryngeal view. To address this, we will repeat the main analysis of the primary outcome for all patients, but will assign failure to the first intubation attempt for patients in whom the operator crossed over from the assigned device to the non-assigned device. Third, we will repeat the main analysis of the primary outcome, including only cases in which primary outcome data from the independent observer is complete (ie, excluding cases in which the operator's self-report of whether there was successful intubation on the first attempt defined the primary outcome for that patient). Fourth, because prior intubating experience may influence success with both devices, we will repeat the main analysis of the primary outcome, excluding cases where the operator had ≤10 total prior intubations. Fifth, because prior experience with using a bougie may influence successful intubation in the bougie group, we will repeat the main analysis of the primary outcome, excluding cases where the operator had ≤5 prior intubations while using a bougie. Sixth, we will perform a sensitivity analysis that defines successful intubation on the first attempt as successful tracheal intubation during the first insertion of the laryngoscope blade, regardless of the number of insertions of a bougie or endotracheal tube.

Analysis of the secondary outcome

For the secondary outcome, severe hypoxaemia (lowest oxygen saturation<80%), we will perform an unadjusted, intention-to-treat comparison of patients randomised to the bougie group versus patients randomised to the endotracheal tube with stylet group, using a χ^2 test.

Analyses of exploratory outcomes

For all prespecified exploratory outcomes, we will conduct unadjusted, intention-to-treat analyses comparing patients randomised to the bougie to patients randomised to the endotracheal tube with stylet. Continuous outcomes will be compared with the Wilcoxon rank sum test and categorical variables with a χ^2 test. Between-group differences in continuous and categorical variables and the associated 95% CIs will be presented.

Handling of missing data

We anticipate that no data on the primary outcome will be missing. When data are missing for the secondary or exploratory outcomes, we will perform complete-case analysis, excluding cases where the data for the analysed outcome are missing. There will be no imputation of missing data for these outcomes. In adjusted analyses, missing data for covariates will be imputed using multiple imputations.

Trial status

The BOUGIE trial is a pragmatic, prospective, multicentre, non-blinded randomised clinical trial comparing use of a bougie to use of an endotracheal tube with stylet for tracheal intubation of critically ill adults in the ED and ICU. Patient enrolment began on 29 April 2019.

Pause in enrolment

Over the first 10 months of enrolment, four patients were enrolled and subsequently found to be prisoners. On 28 February 2020, we paused enrolment to evaluate and improve enrolment procedures with a goal of preventing the enrolment of ineligible patients. The decision was made to extend the pause in enrolment during the early stages of the COVID-19 pandemic when enrolment was felt to be infeasible. Enrolment was resumed on 24 August 2020 with introduction of a new preprocedural 'time out' which requires the verbal recitation of eligibility criteria prior to enrolment to prevent subsequent enrolments of ineligible patients.

Ethics and dissemination

Waiver of informed consent

Critically ill patients undergoing tracheal intubation in the ED or ICU are at significant risk for morbidity and mortality from their underlying illness. Most patients undergoing tracheal intubation in routine clinical care receive intubation using either a bougie or an endotracheal tube with stylet on the first attempt. Any benefits or risks of these two approaches are experienced by patients undergoing tracheal intubation in clinical care, outside the context of research. As a requirement for enrolment in the BOUGIE trial, the patient's treating clinician must believe that either a bougie or an endotracheal tube with stylet would be a safe and reasonable approach for the patient (otherwise the patient is excluded). Therefore, making the decision between the two approaches randomly (by study group assignment) rather than by a provider who thinks either approach is safe and

reasonable for the patient was expected to pose no more than minimal additional risk.

The investigators also determined that obtaining informed consent for participation in the study would be impracticable. Tracheal intubation of acutely ill patients is a time-sensitive procedure. Despite the availability of an informed consent document for the intubation procedure in clinical care, the risks and benefits of the procedure are infrequently discussed and the informed consent document for the procedure in clinical care is infrequently completed before the procedure due to its time-sensitive nature, the impairments induced by the patients' critical illness and the frequent absence of surrogate decision-makers.

Because the study was expected to pose minimal risk and prospective informed consent was considered to be impracticable, a waiver of informed consent was requested and granted from the Single Institutional Review Board at Vanderbilt University Medical Center (reference number 182123). This is consistent with previous randomised trials comparing alternative approaches to tracheal intubation commonly used in clinical care.[7 10 16–21]

Information for patients and families

Information regarding the study is made available to patients and families by at least one of the following mechanisms, with the choice between the mechanisms determined by the local context assessment of the site institutional review board and site principal investigators: (1) a patient and family notification sheet provided to each patient and family following enrolment, informing the patient of their enrolment and describing the study; (2) a patient and family information sheet posted in at least three publicly visible locations within the study unit containing general information about the study and contact information for the research team for additional questions or concerns or (3) a patient and family information sheet provided to each patient and family on admission as part of an 'admission packet' containing general study information and contact information for the research team for additional questions or concerns.

Protocol changes

Any further amendments to the protocol will be recorded on ClinicalTrials.Gov as per SPIRIT guidelines. See online supplemental file 1, section 8, for more details on how protocol changes will be handled.

Dissemination plan

Trial results will be submitted to a peer-reviewed journal and will be presented at one or more scientific conferences.

Author affiliations
[1]Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota, USA
[2]Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA
[3]Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA
[4]Department of Emergency Medicine, University of Colorado Denver School of Medicine, Aurora, Colorado, USA
[5]Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, The University of Alabama at Birmingham, Birmingham, Alabama, USA
[6]Pulmonary Section, Birmingham Veteran's Affairs Medical Center, Birmingham, Alabama, USA
[7]Department of Emergency Medicine, Denver Health Medical Center, Denver, Colorado, USA
[8]Department of Emergency Medicine, Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, USA
[9]Department of Emergency Medicine, The University of Alabama at Birmingham, Birmingham, Alabama, USA
[10]Department of Medicine, Division of Pulmonary, Allergy & Critical Care Medicine, The University of Alabama at Birmingham, Birmingham, Alabama, USA
[11]Department of Pulmonary/Critical Care Medicine, Ochsner Health System, New Orleans, Louisiana, USA
[12]Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington, USA
[13]Department of Emergency Medicine, Lincoln Medical Center, Bronx, New York, USA
[14]Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee, USA
[15]Department of Emergency Medicine, University of Washington, Seattle, Washington, USA
[16]Department of Internal Medicine, University of Iowa Hospitals and Clinics Pathology, Iowa City, Iowa, USA
[17]Department of Medicine, Section of Pulmonary, Critical Care, Allergy and Immunologic Disease, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA
[18]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA
[19]Section of Pulmonary/Critical Care Medicine & Allergy/Immunology, Louisiana State University, New Orleans, Louisiana, USA
[20]Department of Medicine, Division of Pulmonary/Critical Care Medicine, Hennepin County Medical Center, Minneapolis, Minnesota, USA

Twitter Sheetal Gandotra @SGandotraMD, Stacy A Trent @drstrent and Andrew Latimer @alatimer13

Collaborators Non-byline authors: Christopher Barnes, MD (University of Washington Harborview Medical Center); Alicia K. Cupelo, MSW (Denver Health Medical Center); Paige DeVries, BS (Hennepin County Medical Center); Sally Dye, RN (Vanderbilt University Medical Center); Andrea Fletcher, RN (Vanderbilt University Medical Center); Christopher S. Gray, RN (Vanderbilt University Medical Center); Kevin High, RN, MPH (Vanderbilt University Medical Center); Michael C. Kurz, MD, MS (University of Alabama at Birmingham Medical Center); Carol L. Lyle, MPH, PA-C (Denver Health Medical Center); Robert Mitchell, RRT (University of Colorado School of Medicine); Justin Oeth, RN, MSN (Vanderbilt University Medical Center); Erika L.W. Rice, DO (Wake Forest School of Medicine); Sarah W. Robison, MD (University of Alabama at Birmingham Medical Center); Alexandra Schick, MD (Louisiana State University School of Medicine); Jamie Stang, BS (Hennepin County Medical Center); Andrew M. Walters, MD (University of Washington Harborview Medical Center); Nathaniel D. Westphal, MD (Wake Forest School of Medicine). Collaborators: Tak Watase, MD MBA (University of Washington Harborview Medical Center); Bradley Lloyd, RRT-ACCS (Vanderbilt University Medical Center); Vijay Krishnamoorthy, MD, PhD (Duke University School of Medicine); Raquel R Bartz, MD, MMCi (Duke University School of Medicine); William C Fox, MD (Duke University School of Medicine); John Whittle, MBBS, MD, FHEA, FRCA, FFICM (Duke University School of Medicine); Bret D. Alvis, MD (Vanderbilt University Medical Center); Stephanie C. Demasi, MD (University of Alabama at Birmingham Medical Center); Laura E. Goyack, MD (University of Alabama at Birmingham Medical Center); Kristy K. Ford, MD (Wake Forest School of Medicine); Trevor S. Mattox, MD (Wake Forest School of Medicine); Anna Altz-Stamm RN, BSN, CCRN (University of Alabama at Birmingham Medical Center); Cristina Bardita, MD, PhD (University of Alabama at Birmingham Medical Center); Mary Clay Boone RN, BSN (University of Alabama at Birmingham Medical Center); Joe W. Chiles III, MD (University of Alabama at Birmingham Medical Center); Kristina Collins RN, BSN (University of Alabama at Birmingham Medical Center); Abby Drescher RN, BSN (University of Alabama at Birmingham Medical Center); Kevin G. Dsouza, MD (University of Alabama at

Birmingham Medical Center); Janna Dunn, RN, ADN (University of Alabama at Birmingham Medical Center); Stacy Ejem, MD (University of Alabama at Birmingham Medical Center); Josh Gautney, MD (University of Alabama at Birmingham Medical Center); Nicole Harris, RN, ADN (University of Alabama at Birmingham Medical Center); Savannah Herder, RN, BSN (University of Alabama at Birmingham Medical Center); Tamer Hudali, MD, MPH (University of Alabama at Birmingham Medical Center); R. Chad Wade, MD (University of Alabama at Birmingham Medical Center); Rutwij Joshi, MBBS (University of Alabama at Birmingham Medical Center); Daniel Kelmenson, MD (University of Alabama at Birmingham Medical Center); Anne Merrill Mason RN, BSN (University of Alabama at Birmingham Medical Center); Scott R. Merriman, MD (University of Alabama at Birmingham Medical Center); Takudzwa Mkorombindo, MD (University of Alabama at Birmingham Medical Center); Megan Moore, RN, MSN (University of Alabama at Birmingham Medical Center); Jada Nowak, RN, BSN (University of Alabama at Birmingham Medical Center); Kate O'Connor, DO (University of Alabama at Birmingham Medical Center); Sheylan D. Patel, MD (University of Alabama at Birmingham Medical Center); G. Bruno Pereira, MD, PhD (University of Alabama at Birmingham Medical Center); Lisa Sarratt RN, BSN (University of Alabama at Birmingham Medical Center); Tabitha Stewart RN, BSN (University of Alabama at Birmingham Medical Center); William S. Stigler, MD (University of Alabama at Birmingham Medical Center); Kadambari Vijaykumar, MBBS (University of Alabama at Birmingham Medical Center); Gina White RN, BSN (University of Colorado School of Medicine); Anthony Defebio (University of Colorado School of Medicine); Jennifer Friedel (University of Colorado School of Medicine); Feysel Mohamed (University of Colorado School of Medicine); Karina Nava (University of Colorado School of Medicine); Angela Otoo (University of Colorado School of Medicine); Christian Perez (University of Colorado School of Medicine) and Cori Withers (University of Colorado School of Medicine).

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ORCID iDs
Brian Driver http://orcid.org/0000-0002-7141-0256
Matthew W Semler http://orcid.org/0000-0002-7664-8263
Sheetal Gandotra http://orcid.org/0000-0002-5475-9704
Jason R West http://orcid.org/0000-0002-0060-0861
Derek W Russell http://orcid.org/0000-0002-2716-1344

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Bougie or Stylet In Patients Undergoing Intubation Emergently (BOUGIE) trial

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