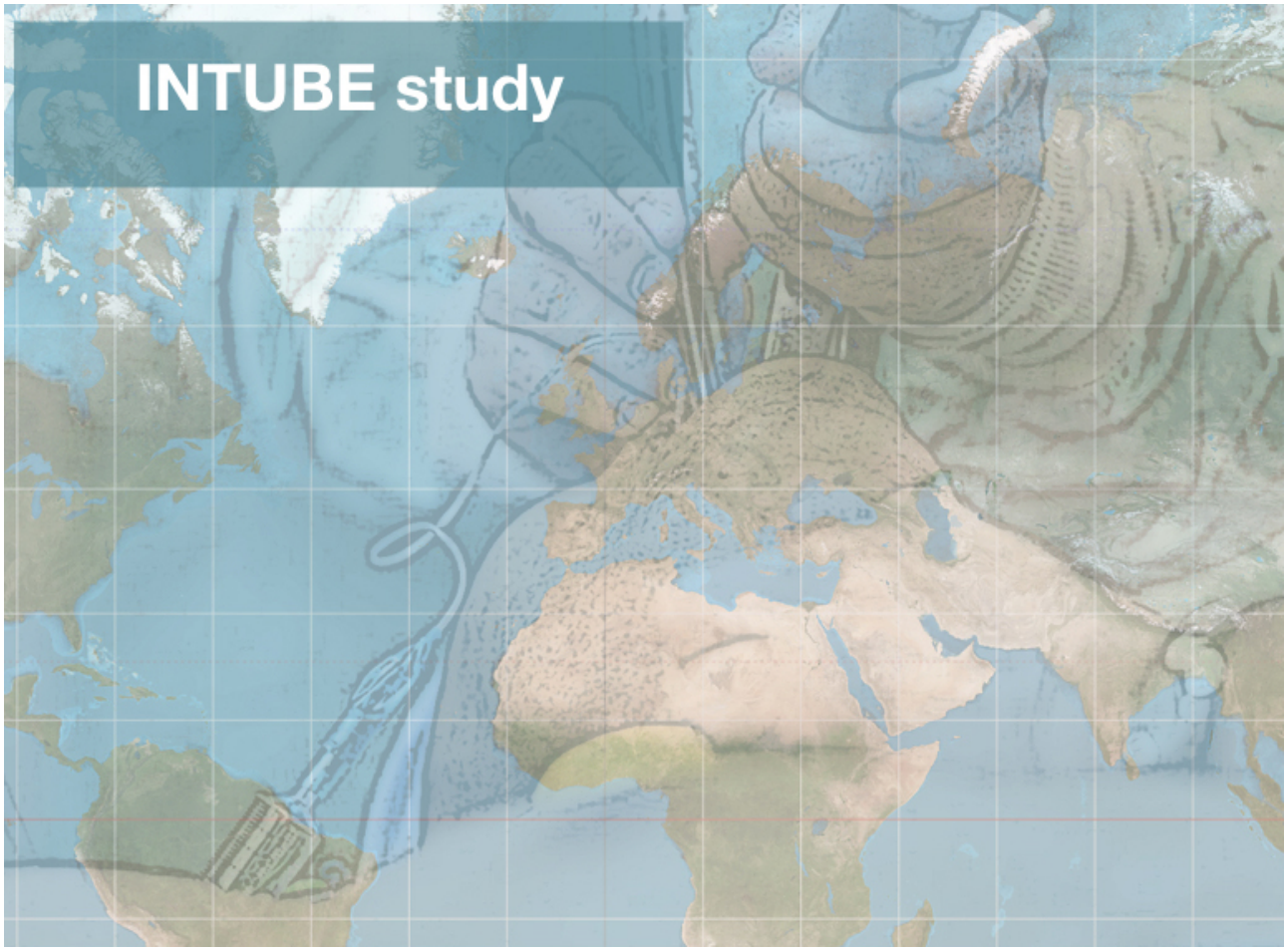

Steering committee:

Vincenzo Russotto (Monza, Italy); vinrussotto@gmail.com
Giacomo Bellani (Monza, Italy)
Giuseppe Foti (Monza, Italy)
Roberto Fumagalli (Milan, Italy)
Antonio Pesenti (Milan, Italy)
Paolo Pelosi (Genoa, Italy)
Luigi Camporota (London)
Philippe R Bauer (Rochester, USA)
Konstanty Szuldrzynski (Cracow, Poland)
Sheila Nainan Myatra (Mumbai, India)
Jonathan Tan Jit Ern (Singapore)
John Laffey (Ireland)
Massimiliano Sorbello (Catania)
Robert Greif (Bern, Switzerland)
Andy Higgs (Cheshire, UK)

INternational observational study **T**o **U**nderstand the impact and **BE**st practices of airway management in critically ill patients

Study acronym identifier: **INTUBE**

Rationale

Endotracheal intubation (ETI) in critically ill patients is a potentially life-threatening procedure and approximately one-third of ETIs is complicated by severe hypoxia, cardiovascular collapse and cardiac arrest [1,2]. Critically ill are prone to severe complications as the consequence of the underlying acute respiratory failure or hemodynamic instability, reduced oxygen stores and increased oxygen consumption [1,3]. Moreover, the rate of difficult airway management may be higher in the intensive care unit (ICU) and in the Emergency Department (ED), prolonging the apnea time and the risk of desaturation [4]. Finally, operator's skills, procedures, devices and drugs, among others, may influence airway management success and patient's outcome [5]. Despite the high risk of the procedure, different interventions lack high-quality evidence and we hypothesize that a heterogeneous practice among different centres and geographical areas may be found [6,7].

The primary aim of our study is to evaluate the incidence of intubation-related adverse events in critically ill patients. Secondary aim is to evaluate current clinical practices on airway management in the in-hospital critical care setting.

METHODS

Study design

Prospective observational multi–centre international cohort study.

Recruitment

We aim at creating a large database on in-hospital airway management practices of critically ill patients from a large and geographically heterogeneous population.

We launched a website: www.intubestudy.com where we will publish study information and documents (e.g. protocol, case report form, national coordinator list) which will be available

for potentially interested investigators. From the website, it will be possible to complete a form for centre and local coordinator(s) data collection. Social media (e.g. *twitter*) will be used to promote the study. Personal connections of the Steering Committee members will be used for study promotion and call for centres. The project will be presented and a call for centres will be announced during international meetings of intensive care.
We will also apply for receiving the endorsement of international scientific societies in order to promote and enhance participation to this study.

Inclusion criteria

We will include all adult (≥ 18 years old) critically ill patients undergoing intubation during the period of observation. We will consider all in-hospital intubations. We will define critically ill those patients with a life-threatening condition requiring intubation for either respiratory failure or airway protection.

Exclusion Criteria

- Intubation performed in the out-of-hospital setting
- Intubation during cardiac arrest
- Intubation performed for anaesthesia (during either diagnostic/endoscopic or surgical procedures)

Primary outcome

At least one of the following (composite outcome):

- Severe hypoxemia (SpO_2 < 80%) occurring within 30 minutes from intubation
- Cardiac arrest occurring within 30 minutes from intubation
- Cardiovascular collapse (at least one of the following), occurring within 30 minutes from intubation:
    - SAP < 65 mmHg recorded 1 time
    - SAP < 90 mmHg for > 30 minutes
    - New need of vasopressors/their increase and/or fluid load > 15 ml/kg to maintain the target blood pressure.

Secondary outcomes

- Difficult intubation (> 2 laryngoscopic attempts)
- Cannot ventilate cannot oxygenate scenario (CICO)
- Emergency front of neck airway (FONA)
- Cardiac arrhythmia
- Aspiration of gastric contents
- Oesophageal intubation
- Pneumothorax/pneumo-mediastinum
- Dental injury
- Airways injury

Long term outcome

- Mortality at ICU-discharge

Data collection

We will collect the following information:

- Informed consent and admission data
- Demographic and clinical characteristics
- Monitoring applied during the procedure
- Reason for intubation/re-intubation
- Ongoing respiratory support before intubation (standard nasal cannula, high-flow nasal cannula, facemask O_2, Venturi system, CPAP, noninvasive positive pressure ventilation)
- Patient's parameters and gas exchange (within 30 minutes) before intubation (arterial pressure, heart rate, SpO_2, vasopressor use, need of colloid/crystalloid administration and total volume, blood gas analysis, GCS, urine output, electrolytes, creatinine and bilirubin levels)
- Chest X-ray findings (if available)
- Operator's training (years of experience, number of endotracheal intubations performed in a week) and duty hours before the procedure
- Characteristics of intubation (anticipated difficult airway management, degree of emergency)

- Intubation procedure (position during preoxygenation, rapid sequence induction applied)
- Preoxygenation method and use of apneic oxygenation
- SpO_2 at the end of preoxygenation
- Drugs used for induction (molecules and doses)
- Elective method for laryngoscopy
- Method used for the second (and following) attempt
- Method used for adequate tube placement confirmation
- Value of first $EtCO_2$ registered
- Duration of laryngoscopy
- Outcome of endotracheal intubation (total number of attempts, laryngoscopic view, minimum SpO_2 during laryngoscopy, need for LMA)
- Major intubation-related complications (severe cardiovascular collapse, severe hypoxemia, cardiac arrest within 30 minutes from intubation)
- Minor intubation–related complications (difficult intubation, supraventricular/ventricular arrhythmia, aspiration of gastric contents, esophageal intubation, dental injury, airway injury pneumothorax/pneumomediastinum, emergent tracheostomy)
- Status at ICU discharge (dead, alive, transferred).

Data will be collected on paper case report forms (CRFs). Local investigators are expected to transcribe all collected data into an interned-based electronic CRF (eCRF, Research Electronic Data Capture – RedCap). Each local investigator will be trained in how to use the eCRF and will receive a personalized username and password. Each patient will be coded through a patient identification number (PIN) generated by the eCRF and no patient names or initials will be present on the paper CRF. Data will be handled confidentially and the paper CRF will be stored behind a lock at each local site. Each centre should keep data stored for the length of the study and the time foreseen by local rules but at least 10 years from the date of study completion.

The paper CRF is attached at the end of this protocol.

Sample size

Our aim is to collect data from at least 1000 major adverse events from airway management.

The reported incidence of at least one major intubation-related complication (severe hypoxia, hemodynamic collapse, cardiac arrest) is approximately 28% [1]. Therefore, we plan to collect data from 3600 intubations.

Intubation rate may vary from 0.5 to 2 ETIs/day according to different centres (e.g. total hospital beds, number of ICUs and ICU beds) and local policies. Each centre will be asked to collect data from 20 ETIs. A maximum time window of 8 weeks will be allowed for each centre (i.e. for centres with a slower recruitment rate, data collection will stop after 8 weeks irrespective of total number of ETIs collected data). Each centre will select a start date for recruitment from 1 October to 31 March 2018. We plan to recruit at least 180 centres worldwide.

Statistical analysis

We will report mean and standard deviation of normally distributed variables and we will compare them using the student T-test. We will report non-normally distributed variables as median and interquartile range, comparing them using the Mann-Whitney U test. Categorical variables will be expressed as proportion and compared using the Chi-square or Fisher exact test as appropriate. We will perform a bivariate analysis to identify variables associated with the composite outcome of major ETI-related complication and significant variables will be then used to construct a multivariate logistic model in order to identify independent variables. A two-sided p-value < 0.05 will be considered statistically significant. Statistical analysis will be performed by the SPSS software package.

Publication and authorship policy

The main results of INTUBE study will be published in a peer–reviewed international medical journal. Authorship policy will follow the International Committee of Medical Journal Editors (ICMJE) recommendations. Authorship will be considered based on contributions to recruitment of patients, data acquisition and cleaning, analysis and interpretation of the data, manuscript writing, submission of national/local grants AND final approval of the version to be published AND agreement to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the

work are appropriately investigated and resolved.

Members of the Steering Committee will be part of the Writing Committee and listed as Authors. National Coordinators and particularly committed investigators fulfilling the previously exposed criteria will be part of the Writing Committee.

Each centre will designate a maximum of two local coordinators who will provide scientific and structural leadership in their centres. They will ensure that all local necessary ethical and regulatory approvals are obtained before start of patient inclusion. Local coordinators will guarantee the integrity of data collection and ensure timely completion of CRFs.

Local coordinators will be listed as study collaborators.

Secondary analyses

After publication of the primary results, on request, the pooled dataset will be available for all investigators for secondary analysis, after judgment and approval of scientific quality and validity by the Steering Committee.

Before submission, the final version of all manuscripts related to the INTUBE study dataset must be approved by the Steering Committee. The members of the Writing Committee will be authors of the publications derived from the INTUBE study dataset.

References

1. Jaber S, Amraoui J, Lefrant J-Y, Arich C, Cohendy R, Landreau L, et al. Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: A prospective, multiple-center study*. Crit. Care Med. 2006;34:2355–61.

2. Russotto V, Cortegiani A, Raineri SM, Gregoretti C, Giarratano A. Respiratory support techniques to avoid desaturation in critically ill patients requiring endotracheal intubation: A systematic review and meta-analysis. J Crit Care. 2017;41:98–106.

3. Mosier JM, Hypes CD, Sakles JC. Understanding preoxygenation and apneic oxygenation during intubation in the critically ill. Intensive Care Med. Springer Berlin Heidelberg; 2017;43:226–8.

4. Martin LD, Mhyre JM, Shanks AM, Tremper KK, Kheterpal S. 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. Anesthesiology. The American Society of Anesthesiologists; 2011;114:42–8.

5. Jaber S, Jung B, Corne P, Sebbane M, Muller L, Chanques G, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Intensive Care Med. 2010;36:248–55.

6. Higgs A, Cook TM, McGrath BA. Airway management in the critically ill: the same, but

different. British Journal of Anaesthesia. 2016;117 Suppl 1:i5–i9.

7. Myatra SN, Shah A, Kundra P, Patwa A, Ramkumar V, Divatia JV, et al. All India Difficult Airway Association 2016 guidelines for the management of unanticipated difficult tracheal intubation in adults. Indian J Anaesth. 2016;60:885–98.