STUDY PROTOCOL
NOSOCOMIAL RESPIRATORY INFECTIONS

Intensive care unit patients with lower respiratory tract nosocomial infections: the ENIRRIs project

Gennaro De Pascale[1], Otavio T. Ranzani[2], Saad Nseir[3], Jean Chastre[4], Tobias Welte[5], Massimo Antonelli[1], Paolo Navalesi[6], Eugenio Garofalo[6], Andrea Bruni[6], Luis Miguel Coelho[7,8], Szymon Skoczynski[9], Federico Longhini[10], Fabio Silvio Taccone[11], David Grimaldi[11], Helmut J.F. Salzer[12,13,14], Christoph Lange[12,13,14], Filipe Froes[15], Antoni Artigas[16], Emili Díaz[16], Jordi Vallés[16], Alejandro Rodríguez[17], Mauro Panigada[18], Vittoria Comellini[19], Luca Fasano[19], Paolo M. Soave[1], Giorgia Spinazzola[1], Charles-Edouard Luyt[4], Francisco Alvarez-Lerma[20], Judith Marin[20], Joan Ramon Masclans[20], Davide Chiumello[21,22], Angelo Pezzi[21,22], Marcus Schultz[23], Hafiz Mohamed[24], Menno Van Der Eerden[25], Roger A.S. Hoek[25], D.A.M.P.J. Gommers[25], Marta Di Pasquale[26,27], Rok Civljak[28], Marko Kutleša[28], Matteo Bassetti[29], George Dimopoulos[30], Stefano Nava[31], Fernando Rios[32], Fernando G. Zampieri[33], Pedro Povoa[7,8], Lieuwe D. Bos[34], Stefano Aliberti[26,27], Antoni Torres[2] and Ignacio Martín-Loeches[24], for the European Network for ICU-related respiratory infections (ENIRRIs)

ABSTRACT The clinical course of intensive care unit (ICU) patients may be complicated by a large spectrum of lower respiratory tract infections (LRTI), defined by specific epidemiological, clinical and microbiological aspects.

A European network for ICU-related respiratory infections (ENIRRIs), supported by the European Respiratory Society, has been recently established, with the aim at studying all respiratory tract infective episodes except community-acquired ones. A multicentre, observational study is in progress, enrolling more than 1000 patients fulfilling the clinical, biochemical and radiological findings consistent with a LRTI. This article describes the methodology of this study. A specific interest is the clinical impact of non-ICU-acquired nosocomial pneumonia requiring ICU admission, non-ventilator-associated LRTIs occurring in the ICU, and ventilator-associated tracheobronchitis. The clinical meaning of microbiologically negative infectious episodes and specific details on antibiotic administration modalities, dosages and duration are also highlighted. Recently released guidelines address many unresolved questions which might be answered by such large-scale observational investigations. In light of the paucity of data regarding such topics, new interesting information is expected to be obtained from our network research activities, contributing to optimisation of care for critically ill patients in the ICU.

@ERSpublications
Methodology for the first European network for ICU-related respiratory infections (ENIRRIs) project http://ow.ly/sud930fU1e7

Cite this article as: De Pascale G, Ranzani OT, Nseir S, *et al.* Intensive care unit patients with lower respiratory tract nosocomial infections: the ENIRRIs project. *ERJ Open Res* 2017; 3: 00092-2017 [https://doi.org/10.1183/23120541.00092-2017].

Received: Sept 05 2017 | Accepted: Sept 17 2017

Clinical trial: This study is registered at clinicaltrials.gov with identifier number NCT03183921.

Support statement: European Respiratory Society (Clinical Research Collaborations (2014)). Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at openres.ersjournals.com

Affiliations: [1]Dept of Anesthesiology and Intensive Care, Università Cattolica del Sacro Cuore, Fondazione Policlinico Agostino Gemelli, Rome, Italy. [2]Institut del Torax, Hospital Clinic, Dept of Pulmonology, University of Barcelona, Institut D'investigacions August Pi I Sunyer (IDIBAPS); Centro de Investigación Biomedica En Red-Enfermedades Respiratorias (CibeRes, CB06/06/0028), Barcelona, Spain. [3]Dept of Intensive Care Medicine, Critical Care Center, CHU Lille, Lille, France. [4]Service de Réanimation Médicale, Institut de Cardiologie, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France. [5]Dept of Respiratory Medicine, Member of the German Center of Lung Research (DZL), Hannover Medical School, Hannover, Germany. [6]Anesthesia and Intensive Care, Dipartimento Scienze Mediche e Chirurgiche, Università della Magna Graecia, Catanzaro, Italy. [7]Polyvalent Intensive Care Unit, São Francisco Xavier Hospital, Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal. [8]NOVA Medical School, CEDOC, New University of Lisbon, Lisbon, Portugal. [9]Dept of Pneumonology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland. [10]Anesthesia and Intensive Care Medicine, Sant'Andrea Hospital, Vercelli, Italy. [11]Dept of Intensive Care, CUB - Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium. [12]Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany. [13]German Center of Infection Research, Borstel, Germany. [14]International Health and Infectious Diseases, University of Lübeck, Lübeck, Germany. [15]Intensive Care Unit, Chest Dept, Hospital Pulido Valente, Centro Hospitalar Lisboa Norte, Lisbon, Portugal. [16]Critical Care Center, Sabadell Hospital, Corporación Sanitaria Universitaria Parc Taulí, Universitat Autonoma de Barcelona, CIBER de Enfermedades Respiratorias (CIBERES), Sabadell, Spain. [17]Critical Care Dept, Hospital Universitari Joan XXIII, IISPV-URV, Tarragona, Spain. [18]Dept of Anesthesiology, Intensive Care and Emergency, U.O.C. Rianimazione e Terapia Intensiva, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy. [19]Alma Mater University, Dept of Clinical, Integrated and Experimental Medicine (DIMES), S. Orsola-Malpighi Hospital, Bologna, Italy. [20]Critical Care Dept, Hospital del Mar, Critical Illness Research Group (GREPAC), Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain. [21]Dipartimento di Emergenza - Urgenza, ASST Santi Paolo e Carlo, Milan, Italy. [22]Dipartimento di Scienze della salute, Università degli Studi di Milano, Milan, Italy. [23]Mahidol Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. [24]Dept of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St. James's Hospital, Dublin, Ireland. [25]Erasmus MC, Rotterdam, The Netherlands. [26]Dept of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy. [27]Internal Medicine Department, Respiratory Unit and Regional Adult Cystic Fibrosis Center, IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milan, Italy. [28]'Dr. Fran Mihaljevic' University Hospital for Infectious Diseases, University of Zagreb School of Medicine, Zagreb, Croatia. [29]Infectious Diseases Clinic, Dept of Medicine University of Udine and Santa Maria Misericordia Hospital, Udine, Italy. [30]Dept of Critical Care, University Hospital ATTIKON, Medical School, National and Kapodistrian University of Athens, Athens, Greece. [31]Alma Mater University, Dept of Clinical, Integrated and Experimental Medicine (DIMES), Respiratory and Critical Care Unit, S. Orsola-Malpighi Hospital, Bologna, Italy. [32]Hospital Nacional Profesor A Posadas, Buenos Aires, Argentina. [33]HCor Research Institute, Hospital do Coração, São Paulo, Brazil. [34]Academic Medical Center, Amsterdam, The Netherlands.

Correspondence: Antoni Torres, UVIR, Servei de Pneumologia, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain. E-mail: ATORRES@clinic.cat

Introduction

The clinical spectrum of lower respiratory tract infections (LRTI) potentially affecting patients managed in the intensive care unit (ICU) includes different diseases with peculiar epidemiological, clinical and microbiological aspects. Different scenarios might be identified by physicians dealing with nosocomial respiratory infections. On one hand, some hospitalised patients may develop nosocomial pneumonia outside the ICU, but then be transferred to the ICU because of the development of organ failure and the need for critical care support: these patients are considered to have non-ICU-acquired nosocomial pneumonia requiring ICU admission [1–3]. On the other hand, the clinical course of patients already admitted to the ICU, for a variety of reasons, may be complicated by the occurrence of a LRTI: these patients are considered to have an ICU-acquired pneumonia (ICUAP). ICUAP may affect patients who are undergoing mechanical ventilation or during spontaneous breathing [4, 5]. Hence, this definition includes both ventilator-associated pneumonia (VAP) and non-ventilator ICU-acquired pneumonia (NV-ICUAP). Furthermore, nosocomial pneumonia may also occur in patients who are noninvasively ventilated in the ICU or in those with a tracheostomy but already weaned from the ventilator: these represent a specific subgroup of patients with NV-ICUAP. Finally, when ICU ventilated patients match the clinical, biochemical and microbiological criteria for VAP without the presence of a new infiltrate on the chest radiographs, a diagnosis of ventilator-associated tracheobronchitis (VAT) may be formulated [6]. All these entities are leading infections in critically ill patients and account for prolonged mechanical ventilation and length of stay, and poor outcome. It has been documented that both VAP and hospital-acquired pneumonia (HAP) are prevalent severe hospital-acquired infections, accounting for more than 20% of all hospital-acquired infections, with an attributable mortality rate ranging between 20% and 50% and an estimated extra-cost of approximately USD 40 000 per patient [7]. However, their relative clinical impact and epidemiological profile is not yet well understood [8–10].

The European Respiratory Society (ERS) is heavily involved in the coordination of investigational activities in respiratory medicine across Europe through its funding of clinical research collaborations (CRCs) aiming to advance scientific and clinical research within a specific disease area (https://www.ersnet.org/research/clinical-research-collaborations). The increasingly relevance ERS is giving to the development of CRCs as a crucial tool to promote networking and research is recognised by the institution of a CRC director as part of the Science Council. Among the CRCs developed within the respiratory infections

assembly of the ERS, a European network for ICU-related respiratory infections (ENIRRIs) has been recently established with the objective of investigating the epidemiological, clinical and microbiological profile of all the respiratory infectious episodes, aside from community-acquired ones, occurring in critically ill patients managed in the ICU. This article describes the methodology of the first project developed as part of ENIRRIs project.

Study methodology

This is a European, multicentre, multinational, prospective, observational study enrolling consecutive critically ill patients affected by nosocomial respiratory infections in the ICU. The following conditions are considered for inclusion in this trial.

1) Out of ICU HAP: hospital length of stay ⩾48 h plus new or progressive radiological pulmonary infiltrate together with at least two of the following: temperature >38°C or <36°C; leukocytosis >12 000 mm^{-3} or leukopenia <4000 mm^{-3}; or purulent respiratory secretions.

2) NV-ICUAP: ICU length of stay ⩾48 h and out of mechanical ventilation ⩾48 h plus new or progressive radiological pulmonary infiltrate together with at least two of the following: temperature >38°C or <36°C; leukocytosis >12 000 mm^{-3} or leukopenia <4000 mm^{-3}; or purulent respiratory secretions.

3) VAP: tracheal intubation/tracheostomy and mechanical ventilation ⩾48 h plus new or progressive radiological pulmonary infiltrate together with at least two of the following: temperature >38°C or <36°C; leukocytosis >12 000 mm^{-3} or leukopenia <4000 mm^{-3}; or purulent respiratory secretions.

4) VAT: As for VAP without a new or progressive radiological pulmonary infiltrate.

The primary objective of the study is to compare mortality among these different pneumonia categories. Secondary objectives are to compare epidemiological patterns with particular emphasis on individual risk factors, microbiological profile, clinical characteristics and therapeutic interventions (*i.e.* severity of the disease and duration of antimicrobial therapy), along with other common outcome measures (*i.e.* length of ICU stay and length of organ support).

All consecutive adult patients admitted to the ICU of participating sites and presenting with nosocomial pneumonia are eligible for the study. Enrolment is performed during a 12-month period, with a maximum of 50 cases per centre. ICUs which take part in the ENIRRIs project agree to prospectively collect the data, clearly document in the medical chart all the information required for the data analysis and transfer the data to the principal investigators of the project. Specific inclusion criteria are: age ⩾18 years; diagnosis of a nosocomial respiratory infection, as defined earlier; admission to either the ICU or a high-dependency unit (the patient may be admitted to the ICU with nosocomial pneumonia or may develop pneumonia during their ICU stay); and informed consent (if required according to local legislation). Case report forms are

FIGURE 1 European network for ICU-related respiratory infections (ENIRRIs) participating centres. Number of centres: Italy n=6; Spain n=5; France n=2; Portugal n=2; Germany n=2; the Netherlands n=2; Belgium n=1; Greece n=1; Ireland n=1; Czech Republic n=1; Poland n=1; Serbia n=1; Croatia n=1; Argentina n=1 (not shown on map); Brazil n=1 (not shown on map).

provided to record the data, and will be electronic and web-based. All epidemiological (type of admission, previous treatments and hospitalisations, previous or other on-going infections, and specific risk factors), clinical (severity of the disease, type and number of organ failures, type and duration of antibiotics, outcome measures) and microbiological information (including the adopted diagnostic approach) required by the electronic case report forms are clearly documented and retrievable from the patient's medical chart (either paper or electronic). All data are anonymous and only the local principal investigator has access to the decoding list in order to link the enrolment number with the corresponding patient. All infections are microbiologically confirmed: sputum in non-ventilated patients, tracheobronchial aspirates (TBA) in intubated/tracheotomised patients, and/or bronchoscopic or blind bronchoalveolar lavage (BAL), within the first 24 h of clinical diagnosis. Diagnostic thresholds are: BAL $\geqslant 10^4$ colony-forming units per mL, and sputum or TBAs $\geqslant 10^5$ colony-forming units per mL, or any threshold if the patient had antibiotic treatment. The final goal of this observational study is to recruit at least 1000 patients across 15 countries, in Europe and Latin America (figure 1). Study results will be disseminated in the form of annual reports, conference abstracts and peer-reviewed publications. The ENIRRIs study group will follow the International Committee of Medical Journal Editors recommendations regarding authorship.

The impact of ENIRRIs research

The epidemiological and clinical evaluation of LRTIs acquired in the hospital setting remains a topic of outstanding relevance. A new definition, a ventilator-associated event (VAE), has been recently introduced in the US scientific debate, grouping all the conditions that result in a significant and sustained deterioration of oxygenation, independent of the infectious nature of the underlying process. However, this definition has been largely observed to be neither sensitive nor specific for VAP, and to be inappropriate for surveillance purposes: the 2016 American Thoracic Society (ATS)/American College of Chest Physicians (ACCP) guidelines have been drafted using only HAP or VAP, and consider VAE, ventilator-associated complications, infectious ventilator-associated complications, *etc.* only as a quality of care indicators [11].

Very little is known about the actual impact of nosocomial pulmonary infections in non-ventilated patients, which represent a large portion of the patients admitted to the ICU with respiratory failure. In this setting, the type of respiratory sampling (invasive *versus* noninvasive) and of microbiological culture (qualitative *versus* semi-quantitative *versus* quantitative) is still a matter of debate.

Furthermore, the latest 2016 ATS/ACCP guidelines recognise several grey areas where recommendations are mostly based on expert opinions (microbiological diagnosis, use of biomarkers, duration of therapy, clinical impact and definition of VAT, and use of inhaled antibiotics). We believe that results from the ENIRRIs study will inform the scientific community and will be of a special help in addressing these clinical and research questions. Importantly, in the absence of any artificial airway (tracheal tube or tracheostomy), the microbiological characterisation of nosocomial pneumonia may be further complicated by the suboptimal reliability of sputum specimens or by the limited feasibility of awake bronchoscopic BAL in spontaneously breathing patients with pneumonia complicated by respiratory failure. However, interventional trials that aim to verify the efficacy of new antimicrobial drugs are focused on both populations (ventilator/non-ventilator-associated pneumonia), testing a complex case mix which includes different types of patients, infections and bacteria [12].

From a microbiological point of view, it is well known that VAP occurring after 96 h of mechanical ventilation (late-onset VAP) is typically caused by multidrug-resistant bacteria and requires a prompt broad-spectrum antibiotic treatment [13]. However, recent data show that a large portion of ICU patients with early-onset VAP are infected with nosocomial flora, since they share many risk factors with long-term ICU admitted subjects. Similarly HAP, NV-ICUAP and VAT may be caused by multidrug-resistant bacteria but, to date, no studies have specifically addressed this topic [14].

Nevertheless, all these pneumonia categories may be clinically confirmed without identifying any pathogen and the clinical relevance and therapeutic approach of such microbiologically negative nosocomial pneumonia is under discussion [15, 16]. Finally, antibiotic strategies, as empirical approach, suggested by current guidelines do not take into account the abovementioned crucial considerations and, although providing general useful indications, may lack validity in many specific settings [16].

In light of the paucity of data regarding this incredibly complex scenario, new insights are absolutely warranted in order to increase our knowledge and improve the outcome of ICU patients with lower respiratory tract nosocomial infections.

This protocol from the ENIRRIs project, along with future upcoming multidisciplinary educational projects and patient–professional collaborations, will contribute to better clarify the clinical impact of such diseases with the aim being to optimise the management of critically ill patients with nosocomial

respiratory infections. Finally, we hope that the results of the ENIRRIs project will help to answer some of the research questions recently posed in the ERS, European Society of Intensive Care Medicine, European Society of Clinical Microbiology and Infectious Diseases and Asociación Latinoamericana del Tórax guidelines for HAP/VAP management [17].

Acknowledgements

ENIRRI is a joint Clinical Research Collaborations (CRCs) project endorsed by the European Respiratory Society (ERS) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID).

References

1 Micek ST, Kollef MH, Torres A, *et al. Pseudomonas aeruginosa* nosocomial pneumonia: impact of pneumonia classification. *Infect Control Hosp Epidemiol* 2015; 36: 1190–1197.
2 Ferrer M, Difrancesco LF, Liapikou A, *et al.* Polymicrobial intensive care unit-acquired pneumonia: prevalence, microbiology and outcome. *Crit Care* 2015; 19: 450.
3 Ranzani OT, Prina E, Torres A. Nosocomial pneumonia in the intensive care unit: how should treatment failure be predicted? *Rev Bras Ter Intensiva* 2014; 26: 208–211.
4 Giunta V, Ferrer M, Esperatti M, *et al.* ICU-acquired pneumonia with or without etiologic diagnosis: a comparison of outcomes. *Crit Care Med* 2013; 41: 2133–2143.
5 Esperatti M, Ferrer M, Giunta V, *et al.* Validation of predictors of adverse outcomes in hospital-acquired pneumonia in the ICU. *Crit Care Med* 2013; 41: 2151–2161.
6 Martin-Loeches I, Povoa P, Rodríguez A, *et al.* Incidence and prognosis of ventilator-associated tracheobronchitis (TAVeM): a multicentre, prospective, observational study. *Lancet Respir Med* 2015; 3: 859–868.
7 Acute lower respiratory infections. *In:* Gibson GJ, Loddenkemper R, Sibille Y, Lundbäck B, eds. The European Lung White Book. Sheffield, European Respiratory Society, 2013.
8 Bassi GL, Ferrer M, Marti JD, *et al.* Ventilator-associated pneumonia. *Semin Respir Crit Care Med* 2014; 35: 469–481.
9 De Pascale G, Bello G, Tumbarello M, *et al.* Severe pneumonia in intensive care: cause, diagnosis, treatment and management: a review of the literature. *Curr Opin Pulm Med* 2012; 18: 213–221.
10 Klein Klouwenberg PM, van Mourik MS, Ong DS, *et al.* Electronic implementation of a novel surveillance paradigm for ventilator-associated events. Feasibility and validation. *Am J Respir Crit Care Med* 2014; 189: 947–955.
11 Kalil AC, Metersky ML, Klompas M, *et al.* Executive summary: management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; 63: 575–582.
12 Niederman MS, Martin-Loeches I, Torres A. The research agenda in VAP/HAP: next steps. *Intensive Care Med* 2017; in press [https://doi.org/10.1007/s00134-017-4695-2].
13 Combes A, Luyt CE, Trouillet JL, *et al.* Controversies in ventilator-associated pneumonia. *Semin Respir Crit Care Med* 2010; 31: 47–54.
14 Timsit JF, Cheval C, Gachot B, *et al.* Usefulness of a strategy based on bronchoscopy with direct examination of bronchoalveolar lavage fluid in the initial antibiotic therapy of suspected ventilator-associated pneumonia. *Intensive Care Med* 2001; 27: 640–647.
15 Torres A, Ewig S, Lode H, *et al.* Defining, treating and preventing hospital acquired pneumonia: European perspective. *Intensive Care Med* 2009; 35: 9–29.
16 Dimopoulos G, Matthaiou DK. Duration of therapy of ventilator-associated pneumonia. *Curr Opin Infect Dis* 2016; 29: 218–222.
17 Torres A, Niederman MS, Chastre J, *et al.* International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. *Eur Respir J* 2017; 50: 1700582.