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Original article

Burden and viral aetiology of influenza-like illness and acute respiratory infection in intensive care units

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Abstract

The purpose of this investigation was to study the viral aetiology of influenza-like illness (ILI) and acute respiratory tract infection (ARTI) among patients requiring intensive care unit admission.

A cross-sectional retrospective study was carried out in Sicily over a 4-year period. A total of 233 respiratory samples of patients with ILI/ARTI admitted to intensive care units were molecularly analyzed for the detection of a comprehensive panel of aetiologic agents of viral respiratory infections.

About 45% of patients was positive for at least one pathogen. Single aetiology occurred in 75.2% of infected patients, while polymicrobial infection was found in 24.8% of positive subjects. Influenza was the most common aetiologic agent (55.7%), especially among adults. Most of patients with multiple aetiology (76.9%) were adults and elderly. Mortality rates among patients with negative or positive aetiology did not significantly differ (52.4% and 47.6%, respectively).

Highly transmissible respiratory pathogens are frequently detected among patients with ILI/ARTI admitted in intensive care units, showing the occurrence of concurrent infections by different viruses. The knowledge of the circulation of several types of microorganisms is of crucial importance in terms of appropriateness of therapies, but also for the implication in prevention strategies and hospital epidemiology.

Keywords: Influenza-like illness; Viral infection; Co-infection; Intensive care units; Sicily; Italy

1. Introduction

According to the World Health Organization (WHO), influenza virus and acute respiratory tract infections (ARTIs) cause considerable morbidity and mortality worldwide, representing close to 20% of all deaths under 5 years of age, particularly in developing countries [1].

Moreover, the elderly or the immunocompromised subjects with influenza-like illness (ILI) or ARTI are at higher risk for exacerbations in pre-existing chronic conditions or progression to respiratory complications, which can be responsible of hospitalization and admission to an intensive care unit (ICU).

It has been demonstrated that several pathogens are implicated in ILI/ARTI, either of viral or bacterial origin, although specific aetiology often goes undiagnosed [2,3]. Patients with acute respiratory illness admitted to the ICU, are usually monitored following a standard approach consisting of routine culture and testing of the bacterial agents commonly responsible of community-acquired pneumonia. Conversely,

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viral agents are generally underestimated in their clinical relevance [4] and laboratory detection is often used as second-line diagnostics or limited to patients negative for other bacterial pathogens, consequently leading to a delayed administration of potentially beneficial antiviral drugs [5].

Additionally, it is well-known that patients showing acute febrile respiratory illnesses may facilitate the spread of infectious agents, especially during the early phase of the disease, often sustained by aerosol-generating procedures able to favor patient-to-patient dissemination in ICU [6] or to healthcare workers (HCWs), visitors, and ultimately the community. This evidence can be further enhanced by well documented low vaccination coverage rates among HCWs versus influenza or other preventable infectious respiratory diseases [7,8], as well as by an inappropriate habit of working while symptomatic for ILI [9].

Although the impact of influenza infection in intensive care wards have been previously described, particularly during the 2009H1N1 influenza pandemic [10], only a limited number of studies have focused on the complex aetiology of ILI/ARTIs in critically ill patients admitted to an ICU.

In this context, a better understanding of a wide spectrum of viral respiratory pathogens causing acute infections among hospitalized patients in these settings is essential for improving preventive and therapeutic strategies and prioritizing diagnostic efforts.

The purpose of this a 4-year cross-sectional study was to evaluate the burden of ILIs and/or ARTIs among hospitalized patients admitted to intensive care units in Sicily and to determine the specific aetiology of respiratory infections.

2. Materials and methods

2.1. Study design and settings

A cross-sectional retrospective study was carried out, from July 2009 to December 2012, on 253 different biological samples (oropharyngeal swabs or bronco-alveolar lavages for intubated patients) consecutively collected from patients admitted to intensive care unit with clinical symptoms of ILI/ARTI. ILI and ARTI were defined according to the European Centre for Disease Prevention and Control (ECDC) (http://ecdc.europa.eu/en/healthtopics/influenza/surveillance/Pages/influenza_case_definitions.aspx; accessed: 17/11/2015). Twenty-two different hospitals located in Sicily, an Italian region with a population of over 5 million people (http://demo.istat.it/pop2013/index.html) participated to the study.

On the basis of the current national healthcare system of Italy, patients were stratified in three different age-groups: ≤14 years, 15–64 years, and ≥65 years (pediatric, adult, and elderly patients, respectively).

A cross-linkage with the Hospital Discharge Records (HDRs) available for the Sicilian Region (Regional Department of Health, Epidemiological Observatory) was performed in order to confirm all information or to obtain additional epidemiological data concerning International Classification of Disease (ICD9-CM) codes, length of hospital stay, and deaths.

Consequently, the study population consisted of patients admitted to ICUs with ILI/ARTI clinical symptoms for whom HDRs included ICD9-CM codes suggestive of ILI/ARTI as primary or secondary diagnosis. The final coding set was selected according to Marsden-Haug and colleagues [11] with the inclusion of ICD9-CM codes for ARTI (i.e. 481, 482.x).

2.2. Detection of respiratory pathogens

Each respiratory specimen was transported at 4 °C and stored at −80 °C upon arrival before processing at the laboratory of the Clinical Epidemiology Unit of the University Hospital “P. Giaccone” in Palermo (Sicily, Italy).

Samples were analysed for the detection of specific viral genomes belonging to human Respiratory Syncytial virus type A (hRSV-A) and B (hRSV-B), Parainfluenza virus 1–4 (hPIV-1/4), Metapneumovirus A (hMPV-A) and B (hMPV-B), Coronavirus OC43 (hCoV-OC43), HKU1 (hCoV-HKU1), NL63 (hCoV-NL63) and 229E (hCoV-229E), Enteroviruses (hEV), Rhinoviruses (hRV), Parechovirus (hPeV), Influenza viruses type A (FluA), B (FluB) and C (FluC), Bocavirus 1–4 (hBoV-1/4), Adenoviruses (hAdV), WU and KI Polyomaviruses (WUPyV and KIPyV). Nucleic acids were extracted from 140 μL of each sample using the QIAamp Viral RNA Mini Kit or the QIAamp DNA Mini Kit (QIAGEN, Milan, Italy) according to manufacturer's protocol.

The detection of respiratory pathogens was performed with singleplex real-time PCR (rPCR) assays using the TaqMan technology and run on a 7000 Real-Time PCR System platform (Applied Biosystems, Life Technologies); primers and probes sets are described in Supplementary Table 1.

For the detection of RNA viruses, we performed RT-rPCR as a single step using the Superscript III® Platinum® one-step Quantitative RT-PCR System (Invitrogen, Life Technologies), while for DNA viruses, the Platinum® Quantitative PCR Supermix-UDG with ROX (Invitrogen, Life Technologies) was used according to manufacturer's instruction.

Each run included positive and negative controls for each target. For FluA and FluB RT-rPCR assays wild type viruses were used as positive controls, whereas for each other target a plasmid standard was used, after cloning into TOPO® TA vector (Life Technologies) a synthetic construct (GeneArt® Gene Synthesis, Life Technologies) or a PCR product.

2.3. Data analysis

Descriptive statistics were calculated to explore both the burden of ILI/ARTI among ICU patients and the distribution of single and multiple aetiology by gender, age, length of hospital stay, and adverse outcomes.

Categorical variables were described as frequencies and percentages and were compared with the chi-square test or Fisher's exact test where appropriate. Continuous variables were presented as the median and interquartile range and compared using the Student *t* test once normality was demonstrated; otherwise, the nonparametric Mann–Whitney U test was performed. Cochran–Armitage test for trend was