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Encephalitis Sentinel Surveillance in Intensive Care Units in Brazil

- Brazil ICU Encephalitis Surveillance -

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1) Introduction

The emergence or reemergence of infectious diseases with major public health impact due to potential severity, such as encephalitis and haemorrhagic fevers, are a challenge for the health systems and health authorities around the world, in an increasingly globalized community, with large mass agglomeration events, or even increased risk of bioterrorism [1,2].

It is believed that new infectious diseases begin to circulate in the population, often with severe cases, long before they are officially described in the literature [3,4]. Thus, Intensive Care Units (ICUs) would be an important target for sentinel syndromic surveillance tools, optimizing resource consumption precisely by focusing on new diseases with greater potential for severe presentations and, therefore, higher associated morbidity and mortality. However, health surveillance in ICUs are still underdeveloped, particularly in low and middle income countries [3].

A passive, vertical and disease-oriented surveillance system may let a large number of undiagnosed cases occur, delaying recognition of outbreaks and identification of new pathogens [5]. Therefore, there is need for syndromic surveillance of cases of *Undiagnosed Severe Infectious Illnes*s (USII) - that is, diseases that lead to ICU admission or death, with characteristics of possible infectious etiology, but without an etiological diagnosis with the investigation routine commonly available [1,6]. Australia [3], the United States of America [1,7–9] and the United Kingdom [6] have already conducted studies on the incidence, epidemiology and etiology of the USII and created network for the early detection and rapid diagnosis of these cases.

Among the USII, encephalitis may be considered the hallmark: it is a severe clinical manifestation associated with many infectious diseases, including recently identified emerging and reemerging diseases [10–12]. Also, the true incidence of these infections is difficult to determine because many cases are unreported, the diagnosis may not be considered, or a specific etiology is never confirmed because the microbiological diagnosis of encephalitis is difficult and expensive, particularly in low and middle-income countries, although these disorders occur with sufficient frequency that clinicians should be familiar with the clinical manifestations, diagnostic techniques, and therapeutic options [11]. In Brazil, ICUs are often without resources to perform initial diagnostic tests for etiologies of CNS disease; frequently such testing is not available until a week or more after admission [13,14].

Our proposal is to develop a sentinel syndromic surveillance strategy to identify encephalitis cases possibly related to emerging pathogens admitted to ICUs in Brazil. “Sentinel” to allow a diagnostic intensive approach on a smaller number of cases, “syndromic” to guarantee a sensitive criterion to include new or unexpected pathogens, and in ICUs to prioritize potentially severe threats. In a resource-limited setting it won’t be possible to monitor and investigate all cases of encephalitis, so a

cost-effective algorithm for early identification of the cases that are most likely to be caused by unusual, unexpected or emerging pathogens must be developed. As universal surveillance of encephalitis is not recommended in Brazil, data on incidence, causes and prognosis is not available, leaving a gap in the understanding of the epidemiology of this central nervous system disease in the country. This study will review cases of encephalitis admitted in the last five years to ICUs in a large metropolitan area. Its results will help understand the epidemiology of encephalitis in Brazil and will provide data to build a strategy for early identification of outbreaks and of emerging infectious diseases.

2) Materials and methods

2.1 Study design

Retrospective cohort study in the metropolitan area of Rio de Janeiro, RJ, Brazil, from 2012-2019.

2.2 Study sample

We willuse data from 35 ICUs (600 beds) of nine hospitals in the metropolitan area of Rio de Janeiro - Brazil (12 million inhabitants in 2018 [15]), from january 2012 to july 2019, covered with the Epimed Monitor database, which routinely registers all admissions in ICUs: the Evandro Chagas National Institute of Infectology (INI), Oswaldo Cruz Foundation (Fiocruz); the seven largest hospitals of Rede D'Or private health corporation - Barra D'Or, Caxias D'Or, Copa D'Or, Niterói D'Or, Norte D'Or, Oeste D'Or and Quinta D'Or -, and the Complexo Hospitalar de Niterói (CHN) hospital, a large private health complex.

The Epimed Monitor system is present in more than 400 hospitals throughout Brazil, with 750 ICUs and 11,000 monitored beds, reaching over 1,000,000 patients within its base (http://www.utisbrasileiras.com.br/en/epimed/)[16]. Based on previous studies [17,18], we expect to identify between 100 and 250 cases of encephalitis.

2.3 Inclusion and Exclusion Criteria

Identification of suspected case of central nervous system infections in the Epimed Database of non-surgical and non-neonatal ICU admissions: risk greater or equal to 10% - sensitivity of 88.69%, a specificity of 85.57%, area under the Receiver Operating Characteristics (ROC) curve of 0.892 (95% confidence interval 0.864 - 0.921, $P<0.0001$) - by the authors` diagnostic prediction tool developed for this study, and will be published.

Suspected cases will have their medical records reviewed. Those who fulfill the diagnostic criteria as follows were included as a case of CNSI:

-Brain abscess or suppurative intracranial infections: diagnosis of brain abscess requires at least one of the following criteria:

•Organism identified from brain tissue

•Abscess on gross anatomic or histopathologic exam

•Two of the following: headache, dizziness, fever, localizing neurological signs, changing level of consciousness or confusion; and one of the following: organism on microscopic examination of brain or abscess tissue, neuroimaging evidence of infection, or diagnostic serology.

-Encephalitis: Involvement of the brain parenchyma by the infectious agent. Diagnosis of encephalitis by Venkatesan et al requires:

•Major criteria: Presence of decreased or altered level of consciousness, lethargy or personality change lasting at least 24 hours and exclusion of encephalopathy due to other non-infectious aetiologies

•Two of the following for possible encephalitis, three of the following for probable or confirmed encephalitis: fever, seizures, new onset focal neurological findings, cerebrospinal fluid (CSF) white blood cell (WBC) count >$10x10^6$/L, abnormal neuroimaging and electroencephalography.

-Meningitis: Patients without criteria for encephalitis, and at least one of the following criteria:

•Organism identified from CSF

•The presence of two of the following: fever or headache, meningeal signs or cranial nerve signs (and hypothermia, apnoea, bradycardia or irritability for those under <1 year of age); and one of the following: increased WBC count (≥5 cells/mm3), increased protein and/or decreased glucose in CSF, an organism on Gram stain or culture, or diagnostic serology.

For the purpose of this study, meningoencephalitis cases were classified as encephalitis. Also, the CNSI were classified according to the time of disease evolution in days20: acute infection: ≤7 day; subacute infection: 8-30 days; and chronic infection: >30 days.

•Etiological confirmation of CNSI: microbiological (direct exam/microscopy, isolation by culture/molecular amplification methods, antigenic or serologic evidence of infection, histopathologic exam) VERSUS clinical confirmation (clinical, epidemiological, radiological/other exams criteria, plus cytological/biochemical analysis of CSF and empirical therapy)

The exclusion criteria were: Participants without CNSI case definition, readmissions during the period of data collection (only the first admission was evaluated), evidence of nosocomial or postoperative neuroinfection, diseases of inflammatory or autoimmune etiology, missing important data for analysis or diagnosis.

2.4 Data collection

Cases classified as suspected central nervous system infections, including encephalitis, will have the medical records reviewed and the information retrieved using the Research Electronic Data Capture (REDCap) tool (www.project-redcap.org), an electronic form service aimed at scientific research, with the appropriate international certification of information security for multicentric studies. Those fulfilling the diagnostic criteria will be included in the study and will have the following clinical and laboratory data collected:

. Age (date of birth), gender, ethnicity

. Date of onset of symptoms, date of hospital admission, date of ICU admission, date of outcome

. Postal Code (ZIP Code) of the residence and/or hotel

. History of international travel in the last 6 months

. History of travel in the country in the last 4 weeks

. Attendance at mass events (e.g. Carnival, Olympic Games, etc.)

. Contact with people with similar clinical features

. Contact with healthy or sick animals

. Consumption of unpasteurized, unusual or processed foods in a homemade way

. Clinical history, comorbidities, use of medications, vaccination history

. Initial diagnosis, final diagnosis, diagnostic tests, instituted treatments

. Etiologic agent, date of diagnosis, reason for late diagnosis (test availability, pathogen characteristics, change in clinical features)

. Presence of organic dysfunctions: respiratory failure - arterial oxygen tension (Pa,O2) of <8.0 kPa (60 mmHg), an arterial carbon dioxide tension (Pa,CO2) of >6.0 kPa (45 mmHg) or both [19]; neurologic deterioration - coma, defined as Glasgow coma scale (GCS) <8 points[20]; acute renal failure, defined by RIFLE Classification System for Acute Kidney [21] - Injury 20 as serum creatinine (SCr) increased >3 times baseline, or SCr ≥4 mg/dL or acute rise ≥0.5mg/dL, or glomerular filtration rate decreased 75%, or urine output <0.3mL/kg/h 24h (oliguria), or anuria 12h; and sepsis, defined by the Sepsis-3 Consensus in 2016 as a life-threatening organ dysfunction caused by a dysregulated host response to infection, including septic shock. Septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level less than 2 mmol/L (18 mg/dL) in the absence of hypovolemia [22].

.Severity and prognostic ICU scores: Simplified Acute Physiologic Score (SAPS) 3, Sequential Organ Failure Assessment Score (SOFA) [23–25].

2.5 Outcome Ascertainment

The outcomes will be classified in four groups:

Early etiological diagnosis (less or equal to 72h after ICU admission);
Late etiological diagnosis;
Discharge without diagnosis;
Death without diagnosis;

We will determine if a group of signs, symptoms, lab results and epidemiological information available in the first three days of hospitalization is associated with the outcomes evaluated.

3) Expected results/deliverables:

- Total number of encephalitis cases in a large network of ICUs; Encephalitis cases/ICU admissions; Undiagnosed encephalitis cases/ total number of encephalitis cases.
- Description of the most common causes of encephalitis in these population and the availability of diagnostic procedures in the ICUs;
- A set of variables present at ICU admission associated with an undiagnosed encephalitis outcome;
- The determination of the number and distribution of ICUs to establish a cost-effective sentinel surveillance system.

4) Perspectives:

Our main goal is to develop an integrated endemic and emerging surveillance strategy to be tested in a future prospective study, when cases will be selected for a deeper laboratory and epidemiological investigation. This first retrospective study is important to support some decisions, like what are the most suitable ICUs to be sentinel sites, how many cases we expect to test and which tests we need to offer to complement the ICUs current etiological investigation. The case definition must have high sensitivity and specificity but also timeliness, to identify as early as possible the cases that should be included.

This study will develop surveillance core functions in ICU, an area underrepresented in Brazilian and in other Latin American countries surveillance systems. It will also provide evidence-based information on the necessary diagnostic resources for encephalitis surveillance, helping to plan support functions like laboratory capacity in resource-limited settings.

5) Ethical aspects

This study was designed according to prevailing ethical precepts and will be submitted for analysis in the INI-FIOCRUZ Research Ethics Committee. Medical records will be consulted by the professionals involved in the study, but the identity of the patients will be preserved in anonymized forms and the researchers guarantee confidentiality in any future publication. Being a retrospective study using data collected in past ICU admissions, there are no discomforts or physical risks associated with this project.

6) Chronogram

Time frame: February 2020 - October 2021

Activities	**Period**
RETROSPECTIVE COHORT STUDY	
Epimed database collection and RedCap form elaboration	DONE
Epimed data analysis	DONE
Inclusion of 3 other hospitals	DONE
Review of medical records	DONE
Final analysis and results	2022

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