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Research Article

Surveillance of the Impact of Antimicrobial Resistance in Hospitalized Children: Protocol for a Retrospective Cohort Study

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ABSTRACT

Background: In an era where the common interest in microbiology is on the silent and scary growth of pathogenic microorganisms, the necessity of trying to understand better these organisms' almost ancient world has not gotten out of our sight-especially those isolated and analysed in the laboratory, from fragile pediatric patients' specimens. Immunocompromised patients in pediatry come from various pathogenetic and pathologic conditions. They are constantly at risk of infections, and because of the intense therapies they are going through sometimes, they can also become reservoirs of certain diseases. The current study strives to investigate the impact of such a risk towards preventing increased hospital Length of Stay (LOS) among immunocompromised pediatric patients as much as increased mortality or premature death.

Methods: The idea is to run a retrospective cohort investigation on current laboratory data to study the trends of infections with resistant bacteria among fragile kids in a pediatric facility based in a developed country. Statistical analysis is to understand the impact of such conditions on the patient's health status from the time of the infection until discharge's time from the hospital or the outcome of therapies.

Prospects: The study hopes to demonstrate that implementing world standard antimicrobial stewardship measures is essential in a stewardship programs close to perfect control, management and surveillance of antimicrobial resistance infections. Many facilities in Low and Middle-Income Countries (LMIC) will benefit from having statistically solid evidence since they lack current literature.

Keywords: Surveillance; AMR; Hospitalized children; Immunocompromised; ASP

BACKGROUND

Bacterial resistance is rising, and little is known about its impact on minority populations of immunocompromised children and adolescents [1].

According to the World Health Organization's (WHO) annual reports on microbial resistance, Antimicrobial Resistance (AMR) is a global threat [2]. AMR develops when a microorganism (bacteria, fungi, virus, or parasite) no longer responds to a drug to which it was initially sensitive [3]. This means that some standard treatments no longer work. Infections are more difficult or impossible to control. The risks of spreading the disease to others continuously grow, and hospitalisation

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increases, with additional economic and social costs involved. Dangers of death become increasingly significant, doubling that of patients with infections caused by non-resistant bacteria [4]. The current opinion of world experts is that not addressing the current and future problems of AMR with emphasis will lead to severe degradation of the global public's health [2]. Most antibiotics currently on the market, used to reverse ongoing resistance trends, are those classified as third-level antibiotics. It is known to be administered only in hospitals [5]. They may be less effective than the primary ones, which are more expensive and, unfortunately, often associated with severe severity of the drug's effects on the patient's condition [6].

Several reports indicate that AMR disproportionately affects all countries [2], low-income countries especially [7], with a higher infection burden while, in effect, limited access to effective therapies. Therefore, the creation of protocols or the strengthening of existing ones in general or in specific contexts, in particular, is essential [8].

Antibiotics are essential in treating most infections. This means there is little or no choice for using this treatment whenever needed [4]. The genuine concern at this point lies in the need to know how to slow the continued spread of antimicrobial resistance and reduce the widespread impact on the subject's health status today and in the short term, especially on the most fragile patients [9].

The European Committee for Antimicrobial Susceptibility Testing (EUCAST) defines antimicrobial resistance in two ways: first, by the population of bacteria that exists before exposure to the antimicrobial agent, and second, by adverse clinical outcomes related to uncontrolled infection, if a patient receives that antimicrobial [10]. A microorganism is defined as resistant if it has an acquired or genetic mutational reluctance mechanism to the drug in question, and clinical resistance, on the other hand, is determined by the level of antimicrobial activity associated with a high probability of therapeutic failure [11]. The same authors state that the clinical breaking point for explaining or qualifying resistance has changed. Exposure of a patient to a drug to which the agents causing the infection are resistant is more likely to generate severe adverse consequences than the exposure of the pathogen alone to a drug to which it is susceptible. Therefore, a clinical surveillance system must be constantly monitored [12]. The standard operating procedure in the routine microbiology laboratory is testing bacteria for antimicrobial resistance to most antibiotics.

Although bacterial infections with antibiotic-resistant strains have become a common issue in the clinical setting and AMR is a constantly evolving problem, it can still be controlled through best practice techniques and be prevented through optimal turn-around times [13]. The pain is so severe that it threatens the achievements of modern medicine, as a post-antibiotic era, where common infections and minor injuries can kill, is a real possibility.

The main challenges facing AMR are social, ecological, intellectual, economic, and political, and therefore need to be addressed from the grassroots at the international level [14].

MATERIALS AND METHODS

Objectives of the study

The study aims to evaluate the impact of AMR infections in hospitalized immune-depressed children by comparing the length of stay in the hospital and the percentage of death.

Primary objectives: To compare the length of stay in immunosuppressed patients with multidrug-resistant germ infections versus immunosuppressed patients who develop non-drug-resistant germ infections.

Secondary objectives: To compare mortality in immunosuppressed patients with multi-resistant germ infections versus immunosuppressed patients who develop non-multiresistant germ infections. To compare the length of stay and mortality in non-immunosuppressed patients who develop multidrug- resistant germ infections versus non-immunosuppressed patients who develop non-Multidrug-Resistant (MDR) germ infections. Describe the antibiotic treatments prescribed in immunosuppressed patients with multi-resistant germ infections. Describe the methods of managing infections from MDR germs in the study population.

Study design

This is a retrospective, single-centre, non-profit observational cohort study. The study will start in December 2022 and will last one year. The study will be conducted according to the following schedule:

1. December 2022-January 2023: data collection.
2. February 2023-December 2023: Analysis, interpretations, and publication of results.

Setting

The study will be conducted at the UOC of Microbiology and Diagnostics Immunology of the Bambino Gesu Pediatric Hospital, with the coordination of Prof. Paola Bernaschi, by the research's collaborator (Co-experimenter) Dr. Danielle Domo, a PhD student in Microbiology, Immunology, Infectious diseases and related pathologies at the University of Rome "Tor Vergata".

Study population

The choice of the study population was inspired by previous studies, mentioning the lack of information in the area of pediatrics. Though the present research only pretends to fill some of the possible gaps, we set up the current limitation to ensure a concise and precise response to one of the priorities of the moment in science. Pediatric patients varied from newborn children from 0 to 6 months to individuals aged up to>/=20 years old when they have been on treatment in a pediatric hospital from birth. To maintain a certain level of uniformity, we defined the maximum inclusion (Table 1), patient age to be 18 years hospitalized in ordinary hospitalization in OPBG between January 1, 2020, and December 31, 2022, and with MDR and non-MDR germ isolations from any anatomical district.

Criteria	Inclusion	Exclusion
Population	-Humans -All sexes -Aged 0 to 18 years Infections with AMR organisms and ESBL-producing organisms. Post-antibiotic era studies on infected populations	-Plants only -Animals only
Outcomes	-It is associated with immune depression (a relative state of fragile health requiring constant or ongoing care). -Impact on ongoing therapy at the time of infection	-Health-related quality of life only outcomes associated with the evaluation of the intervention only reports on analytic methodologies
Study design	-Case-control studies -Cohort studies -Cross-sectional studies -Longitudinal studies -Randomized control trials -Modelling studies -Economic evaluations -Evaluations of intervention reporting the impact of exposure of fragile children to AMR	-Letters -Reviews -Editorials -Conference reports -Case series reports -Evaluations of interventions not reporting the impact of exposure
Language	-English -French -Italian	-All other unfamiliar language to the reviewer

Table 1: Inclusion and exclusion criteria for the systematic review on infections with AMR and ESBL-producing organisms in pediatric populations.

RESULTS AND DISCUSSION

Study outcomes

The length of hospital stay will be evaluated as the study's primary outcome. The length of stay will be calculated as the difference between the end of observation date (discharge or date of death) and the date of first germ isolation of each hospitalization. The immunosuppression status will be defined based on the admission or examination request departments. A Multidrug-Resistant (MDR) germ is defined as pathogen resistant to at least three of the following classes of antibiotics: antipseudomonal carbapenems, antipseudomonal cephalosporins, fluoroquinolones, aminoglycosides, beta-lactam antibacterials +penicillins (piperacillin+tazobactam, ampicillin+sulbactam), monobactams, polymyxins.

As secondary outcomes, the following will be evaluated:

1. Intra-hospital death occurred within the last hospitalization with germ isolation, available in the study period.
2. Length of hospital stay and mortality in non-immunosuppressed patients as previously specified.
3. All antibiotic treatments (ATC: J01) prescribed in immunosuppressed patients before and after the onset of the infection.
4. Type of insulation adopted (A, C, D, I).

Variables

The data useful for the study will be taken from the hospital documentation and the DNLab and include the information mentioned in Table 2.

Type	Collected data
Patients and diseases characteristics	Sesso(sex); Data di nascita(of birth); Data ricovero(recovery); Stato di immunodepressione (Yes/No)(status of immunodepression); Data di isolamento del germe(of isolation of germs); Tipo di germe isolato(type of germ isolation);

	Sito di isolamento(isolation site); Antibiogramma del germe isolato (antibiogram of isolation germ); Data di dimissione(discharge date); Stato alla dimissione (dimesso a domicilio/deceduto)(status of discharge)(discharge home/deceased);

Table 2: Data collected by the study.

Bias

The immunosuppression status will not be defined on a clinical basis but on the ward where the request was made or on the hospital admission ward in the index hospitalization. To minimize possible exposure, unclair references will be addressed to referring clinicians.

Sample size

Few studies have compared the impact of multidrug-resistant germ infections in immunosuppressed patients regarding length of stay. However, a recent survey estimated that the median length of hospitalizations in which infectious episodes from non-multiresistant germs occur in immunosuppressed children admitted to intensive care equals 2, 5 days. Assuming a "pooled standard deviation" of 20, it will be sufficient to include 114 patients in the study (57 per group) to highlight an increase in the length of hospitalisation in immunosuppressed children with MDR germ infections equal to 35 days with an alpha error of 5% and a study power of 90% seen in Table 3.

The sample size calculation was performed using the median and Standard Deviation (SD) according to the method developed by Aidan G. O'Keeffe, Gareth Ambler, and Julie A. Barber, published in BMC Medical Research Methodology in 2017 [15].

Enrolment procedure

Data of patients enrolled in the years listed in DH, outpatient clinics, emergencies, and other reception facilities of the OPBG of Rome.

Collection of materials

Data collection: The above data will be collected on an Excel sheet accessible only to the investigators involved in the study. Accessible only to the Ospedale Pediatrico Bambino Gesu (OPBG), where they will be archived later. However, the research results will be the property of both institutes.

All the information in the "Variables" paragraph will be collected and recorded on an Ad hoc Data Collection Form.

For the study, the data collected for each patient will relate to the variables of interest. The following types of personal data will be processed under Art. 4 n.1 of the GDPR: identification data, contact data, data falling under the "particular" categories of personal data-and in particular, data relating to health and genetic data-under art. 9 of the General Data Protection Regulation (GDPR).

The Promoter guarantees that the data of the patients involved in the study will be processed in a pseudonymised manner and used exclusively for the study, according to the provisions of the protocol and current legislation. To maintain data confidentiality, each patient will be associated with an alpha code-anonymous identification number (centre identification letters and an increasing number, for example, e OPBG01, OPBG02) generated when the patient is first entered into the database.

Each investigator provides suitable technical and organizational security measures to guarantee the confidentiality of identity and data, i.e., to prevent data loss, illicit or incorrect use, and unauthorized access. Only the Data strictly necessary and proportional to the study's object and purpose will be collected, managed, and analysed by the Promoter. Each investigator involved will collect the data of the patients enrolled in the study in a pseudonymised manner and will insert these data in the data Collection Form (CRF) in electronic format, according to the provisions of the Protocol and the applicable legislation.

Data analysis: Patient data codes assigned by the hospital are entered and then used for the anonymization process. Once compiled, the data collection forms must be sent from the satellite centre to the OPBG for the final statistical analyses in the form of an attachment to a message and not as text included in the body of the message and must be protected with encryption

95% CI*	P-value	OR**	Estimate the number of microbial culture investigations at the OPBG per Year.
1.58 to 2.16	<0.001	1.87	+/- 331121

Note: CI: Confidence Interval; OR: Odds Ratio

Table 3: Precision estimate for the selected site.

techniques, accessible *via* a password for opening the file communicated separately.

Data retention: The Promoter and each participant will keep the documentation of the study, including the decoding list, adopting forms of document digitization (or dematerialization) for 20 years from the study's conclusion. Regardless of whether or not the filing of documentation relating to the study concerns personal data (of a particular nature or not), according to the definitions of Regulation (EU) 2016/679 (from now on "RGPD"), the Promoter and each participating Center must adopt all the technical and organizational measures referred to in art. Thirty-two of the GDPR and carry out any security checks required by current legislation and subsequent amendments to protect data, information, and documents (both paper and electronic). The archiving system adopted must be the integrity of data, information, news, and electronic records and their future readability for the entire period envisaged by the conservation obligation. To fulfil this obligation, the Promoter and each participating Entity may use external subjects who manage this archiving obligation.

The Sponsor will keep the study's results, particularly the CRF and other original pseudonymised patients' data, for 20 years after the study's conclusion. In addition, patient files (clinical records resulting from visits to participating centers) will be kept at each centre for the maximum period permitted by law.

The data collected by DNlab will be stored on hospital servers for 20 years.

Data transfer: The Promoter will not transmit data to third parties operating in countries outside the European Economic Area (EEA) or to an international organization that does not offer the same level of protection of personal data guaranteed in the EEA.

Statistical plan: Demographic and clinical characteristics will be used to perform a descriptive analysis of the patients included in the study. Qualitative data will be expressed as counts and proportions, while continuous data will be defined as means, standard deviations, medians, and interquartile ranges. Comparisons between groups will be performed using the Chi-squared or Fisher's exact test for categorical data. Students'*t*-tests and ANOVA will be used for continuous data that follows a normal distribution. At the same time, Wilkoxon's and Kruskall Wallis's tests will be applied for data that is not normally distributed. Data normality will be evaluated through the D'Agostino-Pearson test. If appropriate, multivariate regression techniques will investigate possible associations between variables, adjusting for confounding factors.

CONCLUSION

In conclusion, the authors anticipate that the current research protocol will significantly contribute to achieving its objectives. This project holds the potential to address the critical gap in understanding the impact of antimicrobial resistance on the health status and therapeutic outcomes of immune-suppressed children, providing valuable insights for improved healthcare strategies in this vulnerable population.

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CONFLICT OF INTEREST

There is no conflict of interest between the authors.

ETHICAL CONSIDERATIONS

The principal investigator states that this study is based on ethical principles and good clinical practice. We declare that the OPBG's ethical committee approved the project on 03/01/2022, and the communication was sent to the competent authority (for prospective cohort studies).

ACQUISITION OF AUTHORIZATION AND DATA PROCESSING

This study will use the clinical data of all OPBG patients corresponding to the inclusion criteria. Still, for the 114 patients, no new informed consent will be obtained (refer to the Authorizations of the Privacy Guarantor) for organizational reasons (informing all interested parties involves a disproportionate effort). It is impossible to establish whom to contact at the beginning of the study, and the contact addresses are absent; moreover, the personal data are used only for orientation purposes.

PUBLISHING POLICIES

The study results will be made public as soon as they are available in international conferences, congresses, and indexed journals during the study and at its end.

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