1 Informació General

1.1 Study identification

Títol: International surveillance study for hospital-acquired infection in haemato-oncological patients in PICU (ISHION study).

Codi o número d'identificació del protocol: ISHION study.

Versió i data: versió 2. 05.09.2024

1.2 Promotor identification

Fundació per a la Recerca i la Docència Sant Joan de Déu.

1.3 Participant centers principal researchers

1. Hospital Vall d'Hebron, Barcelona: Montserrat Pujol.
2. Wilhelmina Children's Hospital/University Medical Center Utrecht, The Netherlands: Roelie M. Wösten-van Asperen, Josephus P.J. van Gestel.
3. Universitätsklinik Essen, Essen, Germany: Christian Dohna-Schwake.
4. Ghent University Hospital, Ghent, Belgium: Jef Willems.
5. Aghia Sophia Children's Hospital, Athens, Greece: Eleni Christakou.
6. Pediatric Center Tűzoltó street Department, Budapest, Hungary: Klára Horvath.
7. University Hospital Frankfurt, Goethe University: Michael Merker.
8. University General Hospital of Heraklion, Crete, Greece: Ioannis Goniotakis.
9. University Hospital of Bolonia, Italy: Maria Cristina Mondardini.
10. Sheffield Children's Foundation Trust, Sheffield, UK: Sandeep Budhiraja
11. University Hospital of Padova, Italy: Clauda Maria Bonardi.

1.4 Principal investigators

Hospital Sant Joan de Déu, Barcelona: Iolanda Jordan i Carmina Guitart.

2 Justification

Hospital-acquired infections (HAI) are infections acquired during a hospital stay that were not present either during the incubation period or at the time of the patient's admission. They are infections that occur more than 48 hours after admission. They are the most preventable cause of serious adverse events in hospitalized patients.

The publication in 2000 by the Institute of Medicine (IOM) of "To Err is Human: Building a Safer Health System" identified nosocomial infection as one of the main public health problems and emphasized the importance of implementing nosocomial infection prevention systems to

improve the quality of care in healthcare centres. Based on data from the Spanish Nosocomial Infection Prevalence Study (EPINE) and the Point Prevalence Study (PPS), carried out in various European countries in 2010, it was established that around 7% of hospitalized patients had a care-related infection during the prevalence cut-off, and it was estimated that around 5% of hospitalized patients developed a nosocomial infection during admission.

HAI are a major public health problem; they cause high mortality, prolong hospital stays and increase healthcare costs. According to data estimated by the National Nosocomial Infection Surveillance System (NNIS), during 2002 in the United States there were more than 1.7 million nosocomial infections and around 100,000 deaths per year due to this cause. Healthcare-associated infections were among the 10 most frequent causes of death in that country. Although variable depending on the location and severity of the HAI infection, the recently estimated direct cost of these infections in the United States was in the hundreds of billions of dollars.

Awareness of this issue among healthcare professionals and managers is growing and everyone agrees on the need to implement appropriate surveillance systems and control measures. Epidemiological surveillance is a vitally important tool for identifying, measuring and analysing health problems affecting the population and, on this basis, making decisions aimed at promoting health, preventing disease or, failing that, controlling problems that have already occurred. Epidemiological surveillance is a dynamic process involving data collection, analysis, interpretation and dissemination of results that affect a health problem, with the aim of reducing morbidity and mortality and improving health.

Patient registries are very useful tools for understanding the clinical reality of many processes. This is particularly relevant in more specific processes and pathologies, as is the case of HAI in critical patients admitted to intensive care units (ICU).

The ENVIN registry "NATIONAL SURVEILLANCE STUDY OF NOSOCOMIAL INFECTION IN ICU" is a collaborative, voluntary, multicentre, non-interventional program and study organized by the Working Group on Infectious Diseases and Sepsis of the Spanish Society of Intensive Care, Critical Care and Coronary Units (GTEI-SEMICYUC) developed in 1994.

Since 2002, the program has had a simplified version that allows only patients with any of the controlled infections to be included (ENVIN-HELICS simplified), which has made it easier for more and more ICUs to carry out a continuous registry of their infections. It provides a tool for continuous surveillance of the most important nosocomial infection rates in relation to overall ICU risk factors. In 2004, some reforms were adopted within the program to make it compatible with the European project Hospitals in Europe Link for Infection Control through Surveillance (HELICS), the protocols and outcome of which can be found at: http://helics.univ-

lyon1.fr/helicshome.htm. The whole program ENVIN-HELICS, has similar objectives to ENVIN, but it is carried out at the European level.

Throughout the years of work in this registry, aspects of the surveillance of HAI in ICU have been expanded, providing valuable epidemiological information. Since 2013, the pathological history of patients has been available in the database, which will allow better stratification of risk and a deeper analysis of rates and aetiologies. Another novelty is the information on the application of the packages of measures in the management of sepsis, which will add to the traditional outcome indicators (infection rates, antibiotic use, etc.) the possibility of having process indicators and detecting possible areas for improvement in the treatment of septic patients. This information has been incorporated into the report, both globally and for specific infections. Since 2013, patients from Paediatric Intensive Care Units have also been incorporated into the registry.

The current protocol aims to extend this methodology for being applied to a specific population group: haemato-oncology (HO) patients admitted to PICU. These patients present higher morbidity and mortality and are at higher risk of HAI and Multidrug Resistant (MDR) bacterial infections, which usually lead to a high use of broad-spectrum antibiotics. However, there is scarce data regarding antibiotic stewardship protocols or guidelines in HO patients.

The aims of this study proposal are to extend the investigation of nosocomial surveillance at European level, and to unify the research criteria of other critical conditions in oncological patients such as sepsis and respiratory failure.

The ISHION STUDY “International surveillance study for hospital-acquired infection in haemato-oncology patients in PICU” is a collaborative, voluntary, multicentre, non-interventional study organized by the Working Group of EUROPEAN PAEDIATRIC ONCO-CRITICAL CARE.

For ISHION study, a RedCap® database has been designed, combining the evolved criteria of ENVIN-HELICS plus specific oncological data.

To maintain maximum confidentiality of the data entered in the registry, the authorized users are the physicians responsible for each patient in charge of entering the information on the web page. Currently, data collection is performed using a RedCap® form, which is located on a web server and accessed via the Internet. Access is free (using an individual code) and free of charge after identification and registration of those responsible for each PICU. Participation in the registry is voluntary and data collection is longitudinal and prospective.

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3 Study Hypothesis

Haemato-oncological patients (HO) admitted to Paediatric Intensive Care Units (PICUs) have high morbidity and mortality, are at greater risk of hospital-acquired infections (HAI) and infections by resistant germs, leading to a high use of broad-spectrum antibiotics. However, there are few data on antibiotic management in these patients.

Extending the research of HAI in HO patients at a European level, will provide a large sample to unify research criteria, to identify specific risk factors for HO patients, to promote prevention strategies and to improve the quality of care of HO admitted to PICU.

4 Objective and purpose of the study

The main objective of the study is to record device-associated infections related to the stay of HO patients in paediatric Intensive Care Units, specifically pneumonia associated with mechanical ventilation, bacteraemia's related to vascular catheters, bacteraemia's secondary to other sources and infections related to urethral catheterization.

Secondary objectives are:

- To study risk factors associated with HAI in HO patients.
- To study the aetiology of HAI in HO patients.
- To study the antimicrobial agents used to treat HAI in HO patients.
- To analyse antibiotic stewardship in onco-critical patients.
- To study the antibiotic resistance of the microorganisms producing HAI in HO patients.
- To determine the repercussions of HAI in HO patients.
- To study the case-mix of patients admitted to the PICU.
- To compare the evolution of antibiotic consumption of HO in PICU.
- To provide a tool for each unit to maintain its own surveillance system over time, according to its needs or its pretensions.

4.1 Variables

Summary

1.- Identity and demographical data: constitutes the entry at the time of introducing a new patient, collecting data on affiliation, diagnosis, origin of the patient.

2.- Oncological data: constitutes data on oncological history, treatment received, and response to previous treatments.

3.- General clinical and analytical data and supportive care: constitutes data on clinical and analytical findings during PICU admission.

4.- Hospital-acquired infection data: constitutes data referring to HAI, including microorganisms and antibiotics. Also, data referring to each of the patients' hospital-acquired infections risks, comorbidities and previous colonisation. This data will respond to the main study objective.

5.- Follow-up and outcome: constitutes data on follow-up and outcomes of each patient.

All data collection is detailed in Annex 1.

In the following sections, you will find detailed information regarding specific points of data collection and diagnosis criteria related to hospital-acquired infection.

Hospital-acquired infections

During each patient's study period: until ICU discharge or a maximum stay of 30 days (although infections can be recorded for up to a maximum of 60 days), the following infections related to devices are recorded: Ventilator-associated pneumonia, catheter-related bloodstream

infection, secondary bloodstream infection from other sources, and urinary tract infection related to urinary catheterization.

Primary bacteraemia is also calculated as the sum of bacteraemia of unknown origin and secondary bacteraemia due to catheter-related infection.

Colonisations affecting patients will not be recorded within this section.

Other infections:

The infection module allows for archiving other infections in addition to those included in the national study. This enables each unit, independent of the national study, to record the infections of interest (e.g., community-acquired pneumonia, surgical infections, etc.). The list of infections has been modified to include some not previously recorded. See the end of the manual for the list of infections.

Data entry and variable definition:

Infection Date: The date on which the clinician determines that the patient has an infection. In the case of community-acquired infections, the acquisition date cannot be later than the hospital admission date. If the diagnosis is made after admission but within 48 hours (i.e., community-acquired or extra-ICU infections), the infection start date will be the day of admission.

Infection Origin:

- ICU-acquired: When, in the clinician's judgment, signs of infection appear during the patient's stay in the ICU.
- Extra-ICU: When, in the clinician's judgment, signs of infection appear during the patient's hospital stay before admission to the ICU.

Location: It is a dropdown list, so when you click on the arrow on the right side of the field, all possible locations appear. Click the left mouse button to choose the selected option. You always have the option to select "OTHER LOCATION" or "OTHER INFECTION" if the current infection does not correspond to any on the list. The list also includes febrile syndromes treated with antibiotics (not mandatory for the national study).

When selecting the option "Secondary bloodstream infection from catheter-related infection," two windows open: catheter type (central venous, arterial, and peripheral) and insertion site (subclavian, femoral, basilic, axillary, jugular, radial, others). Only the catheter considered (based on tip cultures) as the source of the infection should be selected, even if the patient may have multiple catheters (for example, arterial and venous).

Bacteraemia: When filling in an infection that is a bloodstream infection, the program

automatically selects "Yes."

When a non-bloodstream infection is also bacteraemia (only in the case of pneumonia and urinary tract infections), "Yes" should be filled in for bacteraemia. In this case, a new infection is automatically generated as a secondary bacteraemia. Therefore, it will be necessary to fill in the aetiology of the infection (pneumonia or urinary tract infection) and also another form filling in the aetiology of the secondary bacteraemia (respiratory or urinary, respectively).

For other infections not covered in the ENVIN, if the infection causes bacteraemia, a message appears: "If this infection is bacteraemia, it should be defined as Secondary Bacteraemia."

Sample: Choose the relevant option from those offered. "NO SAMPLE OBTAINED" can be chosen when no sample has been obtained for etiological diagnosis. If there is a sample, it is important to report the microorganism or indicate that the culture was negative.

Clinical Diagnosis: Choose the relevant option from those offered. Only fill in for pneumonia cases. If it is another infection, this variable will remain inactive.

Exposure to the specific risk factor in the 48 hours preceding the infection (mechanical ventilation, urinary catheterization, central venous catheterization): Mark "Yes" if applicable.

Has the patient received antibiotic treatment for this infection? Mark “Yes” if the infection has been treated with antimicrobials.

Is the treatment appropriate according to the antibiogram? Mark “Yes” if the patient has received appropriate empiric antibiotic treatment for this infection at any time, considering appropriate treatment to be when the microorganism being treated is sensitive to at least one administered antibiotic. Mark "Not Applicable" when there is no microorganism and/or antibiogram available or the treatment is specific.

Was the antibiotic treatment adjusted? The term "adjusted" refers to substituting one antibiotic with another of narrower spectrum or discontinuing some of the antimicrobials once the antibiogram is received. Mark "Not Applicable" when there is no microorganism and/or antibiogram available.

Inflammatory Response

The definitions from the 1991, 2003 and 2020 Consensus Conferences will be used.

"Sepsis" is defined as any documented or suspected infection with two or more of the following criteria:

- Fever (core temperature >38.3°C) or Hypothermia (core temperature <36°C)
- Heart rate >90 beats per minute

- Respiratory rate >30 breaths per minute
- Altered mental status.
- Oedema or positive fluid balance >20 ml/kg in 24 hours
- Hyperglycaemia (plasma glucose >110 mg/dl) in the absence of diabetes
- Leucocytosis (>12,000/mm3) or leukopenia (<4,000/mm3) or normal count with >10% immature forms
- Elevated levels of C-reactive protein or procalcitonin in plasma
- SvO2 >70% or cardiac index >3.5 L/min/m2
- "Severe sepsis" is defined as a sepsis episode associated with organ dysfunction, hypoperfusion, or hypotension attributable to sepsis.
- Hypoxemia with PaO2/FIO2 <300 mmHg
- Oliguria (urine output <0.5 ml/kg/hr for at least 2 hours)
- Creatinine increase >0.5 mg/dl or value >2.0 mg/dl
- Coagulation disorder (INR >1.5 or aPTT >60 seconds)
- Thrombocytopenia <100,000/mm3
- Hyperbilirubinemia (bilirubin >2.0 mg/dl)
- Hyperlactatemia (>3 mmol/L or 24 mg/dl)
- Arterial hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <70 mmHg, or a decrease in systolic blood pressure >40 mmHg)

"Septic shock" is defined as persistent arterial hypotension that cannot be explained by causes other than sepsis and does not respond to adequate volume resuscitation.

Microorganisms.

After completing and saving a new infection, a list of the entered infections appears. To enter the microorganism, select the infection from the + icon. On the same page, a new box ADD MICROORGANISM appears (Save even if the culture is negative).

The microorganism can be selected from the dropdown list (see appendix) or you can enter the initial letters of the microorganism, and the possibilities will be searched based on those letters, and finally select the appropriate one.

The number of colony-forming units should be filled in when that information is known.

After selecting a microorganism, the antibiogram is marked, where another screen appears with the antibiotics corresponding to that microorganism. The antibiotics that must be completed are marked in red and with an asterisk, even if it is filled in as "Not done."

When the antibiotic is reported as "intermediate," it will be included in the resistant category.

The following are the ten different antibiograms, the microorganisms that can activate them,

and the required antibiotics for each of them:

1. Pseudomonas Antibiogram: Pseudomonas aeruginosa, Burkholderia (Pseudomonas) cepacia, Pseudomonas mallei, Pseudomonas pseudomallei, Pseudomonas putida, Pseudomonas stutzeri, Pseudomonas others, Pseudomonas spp. Required antibiotics: amikacin, ceftazidime, cefepime, piperacillin-tazobactam, imipenem-cilastatin, meropenem, ciprofloxacin, levofloxacin, and colistin-colimycin.
2. Acinetobacter Antibiogram: Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Acinetobacter lwoffi, Acinetobacter spp. Required antibiotics: imipenem-cilastatin and ampicillin-sulbactam. Recommended: amikacin, colistin-colimycin, and tobramycin.
3. Enterobacteria Antibiogram: Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Klebsiella ozaenae, Klebsiella spp, Proteus mirabilis, Proteus penneri, Proteus vulgaris, Proteus spp, Enterobacter aerogenes, Enterobacter agglomerans, Enterobacter cloacae, Enterobacter sakazakii, Enterobacter spp, Citrobacter diversus, Citrobacter freundii, Citrobacter spp, Moraxella catharralis, Moraxella spp, Salmonella enteritidis, Salmonella paratyphi, Salmonella typhi, Salmonella others, Salmonella spp, Serratia ficaria, Serratia liquefaciens, Serratia marcescens, Serratia rubidaea, Serratia spp, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Shigella spp. Required antibiotics: amoxicillin-clavulanic acid, cefotaxime-ceftriaxone, and ciprofloxacin. Recommended: cefepime, gentamicin, amikacin, piperacillin-tazobactam, imipenem-cilastatin, meropenem, levofloxacin, ceftazidime, and aztreonam.
4. Stenotrophomonas Antibiogram: Stenotrophomonas (Xanthomonas) maltophilia. Required antibiotic: cotrimoxazole (trimethoprim-sulfamethoxazole).Recommended: cefepime, amikacin, ceftazidime, ciprofloxacin, tigecycline, levofloxacin, and colistin-colimycin.
5. Staphylococcus Antibiogram: Staphylococcus aureus, Methicillin-resistant Staphylococcus aureus (MRSA), Staphylococcus epidermidis, Coagulase-negative Staphylococcus, Staphylococcus saprophyticus, Staphylococcus others. Required antibiotics: oxacillin-methicillin and vancomycin. Recommended: teicoplanin, linezolid, gentamicin, rifampicin, levofloxacin, cotrimoxazole (trimethoprim-sulfamethoxazole), tigecycline, mupirocin, and daptomycin.
6. Enterococcus Antibiogram: Enterococcus avium, Enterococcus durans, Enterococcus faecalis, Enterococcus faecium, Enterococcus spp. Required antibiotics: ampicillin and vancomycin. Recommended: teicoplanin, levofloxacin, linezolid, and tigecycline.

7. Streptococcus Antibiogram: Streptococcus spp, Streptococcus pneumoniae, Streptococcus pyogenes, Viridans group Streptococcus, Streptococcus mitis, Streptococcus sanguis, Streptococcus others. Required antibiotics: penicillin and cefotaxime-ceftriaxone. Recommended: cotrimoxazole (trimethoprim-sulfamethoxazole), ciprofloxacin, levofloxacin, linezolid, and tigecycline.
8. Haemophilus Antibiogram: Haemophilus ducreyi, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus spp. Required antibiotics: ampicillin, amoxicillin-clavulanic acid, cefotaxime-ceftriaxone, and ciprofloxacin. Recommended: aztreonam and levofloxacin.
9. Candida spp Antibiogram: Candida albicans, Candida spp, Candida tropicalis, Candida krusei, guilliermondii, Candida glabrata, Candida kefyr.Candida auris. Required antibiotics: amphotericin and fluconazole. Recommended: voriconazole, caspofungin, itraconazole, and 5-fluorocytosine.
10. Aspergillus Antibiogram: Aspergillus spp, Aspergillus fumigatus, Aspergillus niger, Aspergillus terrens, Aspergillus flavus, Aspergillus nidulans. No required antibiotics. Recommended: amphotericin, voriconazole, caspofungin, and itraconazole.

The effectiveness of each antibiotic against the studied microorganism is evaluated in one of the following three categories:

- Sensitive: Evaluated as such by the Microbiology Laboratory regardless of the method used.
- Resistant: This category includes non-sensitive and intermediate results.
- Not done: When the result is not available for any reason.

<u>Antimicrobials.</u>

Antibiotic: Select from the options in the list or enter the first letters of the antibiotic, and the possibilities will be searched based on those letters until the appropriate one is selected.

Start date: The date when the administration begins, even if it occurs before admission to the ICU. If the start date is unknown, enter the date of ICU admission. Key field (cannot be modified).

End date: The date when the administration ends.

If the administration of an antibiotic is interrupted for 24 hours for any reason, the end date will be considered as the definitive end of treatment.

If the patient is discharged with antibiotic treatment, the ICU discharge date will be considered as the end date.

- Indication: Select one of the following categories:

- Extra-ICU nosocomial infection: When, in the clinician's judgment, signs of infection appear during the hospital stay before admission to the ICU.
- Intra-ICU nosocomial infection: When, in the clinician's judgment, signs of infection appear during the ICU stay.
- Surgical prophylaxis: The antibiotic is prescribed to prevent the occurrence of infections related to surgical procedures. In general, this prophylaxis is of short duration. The appropriateness of the criteria, duration, or antibiotic is not evaluated.
- Other prophylaxis: When, in the clinician's judgment, the antibiotic is used for prophylaxis and there is no evidence of present infection. Examples include prophylaxis for skull base fractures, pancreatitis, non-infected open wounds, etc. These prophylaxes are usually longer than post-surgical prophylaxes.
- Unknown: When the administration of the antibiotic cannot be attributed to any of the causes.

If the response is prophylaxis, the 'Treatment reason' variable is deactivated.

Infection: Select the infection for which the antibiotic treatment is intended. It is not activated if the indication is prophylaxis or unknown. The same list as the infection's module is displayed. If antibiotics have been administered without being able to determine the focus, select "febrile syndrome treated with antibiotics" or "infection without focus" depending on whether the patient only has fever, or a more complex condition accompanied by systemic inflammatory response syndrome.

Treatment reason: Choose one of the two options.

- Empirical treatment: When the antibiotic is prescribed without knowledge of the etiological agent.
- Directed treatment: According to the results of microbiological sensitivity (antibiogram).
- If the treatment is directed, the 'Treatment confirmation' variable is blocked.
- Confirmation: Choose one of the following possibilities.
- Yes, it is appropriate: The results of the conducted cultures confirm that the antibiotic is appropriate and has been administered properly.
- No, it is not appropriate: The results of the conducted cultures confirm that the antibiotic is NOT appropriate or has not been administered properly.
- Negative cultures: The results of the conducted cultures are negative.
- No cultures requested: No samples have been sent for etiological study.
- Not an infection: This option is marked when, based on initial studies, it is concluded

that the clinical condition does not correspond to any infection.

- Antibiotic change: Choose one of the options. A change is considered intentional modification of antibiotic treatment for one of the following reasons:
- Not covered: If the pathogen has decreased sensitivity or resistance to the prescribed antibiotic.
- Spectrum reduction: When, even if it is sensitive, it is decided to modify the antibiotic by choosing another antibiotic with a narrower spectrum of action that covers the pathogen causing the infection.
- Resistance during treatment: When it is considered that the microorganism persists after the treatment has started due to the emergence of resistance to the administered antibiotic.
- Poor clinical evolution: When, despite the pathogen being sensitive to the administered antibiotic, the clinical evolution is deemed poor, and a decision is made to switch to another antibiotic.
- Toxicity (adverse effects): When the antibiotic needs to be replaced due to allergic or toxic effects.
- Other: In situations not covered by the above categories.

Monthly factor table.

For the ISHION study, the monthly factor table MUST be filled in. This table is accessed from the home page, not from the patient's admission form, since it refers to factors collected from the whole unit. A message will warn of the need to fill in the monthly factor table when a patient has been entered.

Mode of completion. Each item should be counted daily, preferably at the same time, and entered in its corresponding box.

One sheet should be used for each calendar month or fraction thereof. The data for each day correspond to one row.

Definition of the variables (in order of completion)

- New patients: All patients who have been admitted the previous day and remain admitted at the time of data collection.
- Admitted patients: Number of patients admitted at the time of data collection.
- Patients with antibiotic: Number of patients who are receiving systemic antibiotics (either for treatment or prophylaxis), thus excluding topicals (e.g. those on DDS protocols).
- BMR patients: Number of patients who are infected or colonized by multi-resistant

bacteria.

- Isolated patients: Number of patients with contact precautions regardless of the reason for this isolation, i.e. for prophylaxis (e.g. neutropenic patients or patients pending ruling out multidrug-resistant colonization) or because they are already colonized / infected.
- Patients with airway: The number of patients intubated or with tracheostomy at the time of data collection should be recorded.
- Patients with a urinary catheter: The number of patients with a urinary catheter at the time of counting will be recorded. Urinary catheters will be considered as those inserted by transurethral route as well as those inserted by bladder size or nephrostomy.
- Patients with AC (Arterial Catheters): The number of patients with systemic arterial catheters at the time of counting will be recorded.
- Patients with CVC (Central Venous Catheters): The number of patients with central venous catheter(s) at the time of counting will be recorded. A central catheter is considered as any catheter located in large veins, regardless of its use.
- This includes "drum or PICC" type catheters cannulated via the basilic or cephalic route (called peripherally inserted central catheters), as well as independently cannulated transient pacing catheters.

A central venous catheter is defined as an intravascular catheter that reaches or is close to the cardiac cavity or is within one of the large vessels used for infusion, blood withdrawal or hemodynamic monitoring.

The following are considered large vessels for the purpose of reporting CVC infections: superior vena cava, inferior vena cava, brachiocephalic veins, internal jugular vein, external iliac vein, and the common femoral vein.

Extrinsic risk factors

For the national study and for HELICS level I, this section will only be completed voluntarily by each unit. However, it provides individual patient information, so it is highly recommended to complete this section. In this section, the important aspect is the periods of time during which a specific risk factor was present.

The variable definitions will be the same as those used in the main form. For risk factors, the use of an artificial airway is more important than mechanical ventilation itself, so the duration of artificial airway usage will be recorded. Non-invasive mechanical ventilation is considered when the patient receives some form of mechanical respiratory assistance without intubation or

tracheostomy (BiPAP, CIPAP). Nasogastric tube refers to all tubes used for extraction or nutrition purposes (nasogastric, nasoduodenal, or naso-jejunal), and enteral nutrition administration refers to the administration of nutrients through a gastric or enteral tube.

The start date (first day) and end date (last day) of each risk factor will be recorded. If the patient is discharged with any extrinsic factor (catheter, urinary catheter, etc.), the discharge date will be noted. It may be necessary to record the start date of a device before admission to the ICU. This can be noted, although when calculating the days of risk factors for the national study, it will be counted from the ICU admission date.

For artificial airway and the presence of central venous catheters, there are up to 3 possibilities to be filled in when the patient has interrupted mechanical ventilation or catheter usage for more than 24 hours; that is, there is an intermediate period of more than 24 hours without the risk factor.

For central venous catheters, what matters is the start and end dates during which the patient has one or more central venous catheters. When changing the catheter location on the same day, it is not necessary to record the change. It should be noted that two simultaneous catheters do not count as two, but as one.

The tracheostomy and reintubation dates are the dates on which the procedures are performed.

For some less important factors (enteral nutrition, parenteral nutrition, arterial catheter, etc.), only one period has been considered, so the start date to the end date will be recorded globally, even if there were interruptions in between. For the nasogastric tube, only the start date has been considered.

<u>Colonisation</u>

In the 19th form of the database, there are the variables related to HAI previous colonisation. Find the explanation regarding colonisation and infection diagnosis criteria and data collection.

In this section all patients who have an infection or colonization by multiresistant microorganisms will be noted. There are three possibilities:

1. Previous: When the patient is known to be colonized or infected by these pathogens prior to admission to the ICU.
2. During: When this infection or colonization is acquired during admission to the ICU.
3. No (default): When you do not have colonization/infection by multidrug-resistant pathogens.

- MRSA (MRSA): For all cases in which the patient has presented colonization or infection by methicillin-resistant Staphylococcus aureus before or during his/her stay in the ICU. It is differentiated whether this colonization or infection is prior to

or during admission to the ICU.

- Vancomycin-resistant Enterococcus: For all cases in which the patient has presented colonization or infection by vancomycin-resistant Enterococcus before or during his/her stay in the ICU. It is differentiated whether this colonization or infection is prior to or during admission to the ICU.
- Multidrug-resistant Pseudomonas: For all cases in which the patient has presented colonization or infection by Pseudomonas with resistance to 3 or more families of antibiotics (Carbapenems, Cephalosporins, Piperacillin-Tazobactam, Quinolones, Aminoglycosides) before or during their stay in the ICU. It is differentiated whether this colonization or infection is prior to or during admission to the ICU.
- Acinetobacter R-Imipenem: For all cases in which the patient has presented colonization or infection by carbapenem-resistant Acinetobacter sp. before or during his/her stay in the ICU. It is differentiated whether this colonization or infection is prior to or during admission to the ICU.
- Enterobacteriaceae BLEE: For all cases in which the patient has presented colonization or infection by extended-spectrum beta-lactamase-producing enterobacteria before or during their stay in the ICU. In general, it is considered that those enterobacteria that are resistant to 3rd generation cephalosporins are beta-lactamase producers and would fall under this definition. It makes a difference whether this colonization or infection is prior to or during admission to the ICU.
- BGN Carbapenemase: For all cases in which the patient has presented colonization or infection by gram-negative bacilli producing metallo-beta-lactamase (which confer resistance to carbapenems and all types of beta-lactams except monobactams) before or during their stay in the ICU. It is differentiated whether this colonization or infection is prior to or during ICU admission.
- Multiresistant BGN: For all cases in which the patient has presented colonization or infection by Gram-negative bacilli with resistance to 3 or more families of antibiotics. This includes other GNB not included in the previous categories (e.g. Stenotrophomonas) that meet this condition. It is differentiated that this colonization or infection is prior to or during admission to the ICU. It is differentiated that this colonization or infection is prior to or during ICU admission.
- Clostridium difficile: For all cases in which the patient presents Clostridium difficile infection determined by the usual microbiological methods and requires isolation and treatment. It is differentiated that this colonization or infection is prior to or during admission to the ICU.

- Tuberculosis: For all cases in which the patient has tuberculosis infection requiring isolation and treatment. It is differentiated whether this colonization or infection is prior to or during admission to the ICU.

It should be considered that there may be more than one response for the same pathogen, e.g. multiresistant Pseudomonas and metallo-beta-lactamase, and that both should be filled in.

For each of the resistant microorganisms, when infection/colonization is considered, the location of the infection or colonization should be filled in according to a drop-down list. Only one focus will be included (although there may be several) prioritizing the primary focus or the most important one. For example, a bacteraemia pneumonia, put pneumonia; a bacteraemia and the culture of the same bacteria in an abdominal drainage put blood.

For each of the resistant microorganisms acquired during admission to the ICU, the date on which it was detected should also be filled in.

When both possibilities (colonization or infection) occur in the same patient, the following criteria will be followed:

1. If there is previous colonization / infection, it is prioritized against the one acquired in ICU. For example, a patient who is admitted to the ICU with MRSA colonization and acquires an MRSA infection in the ICU, the previous MRSA colonization is prioritized.
2. Infection is prioritized over colonization.
3. For each pathogen, only one focus will be included, even if there are several infections or colonisations. The focus that presupposes greater severity will be chosen (e.g., blood on abdominal drainage).

5 Study design

Multicentre, observational and prospective study.

5.1 Study period

During two complete years.

5.2 Follow-up period of the study subjects

From admission to the PICU until discharge from the PICU.

The maximum follow-up period of a patient for the ISHION study will be 60 days. If desired, monitoring can be completed during the entire PICU admission.

For the bacteraemia zero, pneumonia zero and resistance zero projects, the follow-up time is until the patient is discharged from the PICU; therefore, if these records are followed, the infections should be collected regardless of the time the patient is admitted.

5.3 Infections under study

For the present study Intra-PICU infections under study are:

- Ventilator-associated pneumonia (VAP)
- Catheter-associated urinary tract infection (CAUTI)
- Bacteraemia of unknown origin
- Bacteraemia secondary to catheter infection: central line-associated bloodstream infection (CLABSI).
- Bacteraemia secondary to other foci.

5.4 Definitions

Hospital-acquired infections definitions follow CDC criteria.

Central line-associated Bloodstream infection (CLABSI): a laboratory confirmed bloodstream infection (LCBSI) where an eligible bloodstream infection organism is identified, and an eligible central line is present on the LCBI date of event or the day before.

Ventilator-associated pneumonia (VAP): a pneumonia where the patient is on mechanical ventilation for > 2 consecutive calendar days on the date of event, with day of ventilator placement being Day 1* AND the ventilator was in place on the date of event or the day before.

*If the ventilator was in place prior to inpatient admission, the ventilator day count begins with the admission date to the first inpatient location. If a break in mechanical ventilation occurs for at least one full calendar day, ventilator day count for ventilator association starts anew upon reintubation and/or re-initiation of mechanical ventilation.

Catheter-associated urinary tract infection (CAUTI): A UTI where an indwelling urinary catheter (IUC) was in place for more than two consecutive days in an inpatient location on the date of

event or the day before, with day of device placement being Day 1*. If an IUC was in place for more than two consecutive days in an inpatient location and then removed, the date of event for the UTI must be the day of device discontinuation or the next day for the UTI to be catheter-associated.

*If the IUC was in place prior to inpatient admission, the catheter day count that determines catheter association begins with the admission date to the first inpatient location allowing for consistency with device denominator count collection

6 Participant selection

6.1 Recruitment procedure

The patients under study are all those HO patients admitted for more than 24 hours in the Paediatric Intensive Care Units. The study period is over each year and the follow-up period of the study subjects is from admission to the PICU until discharge from the ICU. The maximum follow-up period for a patient is 60 days. Each PICU implements the therapeutic measures that are established in those units according to the pathology of each patient.

A user's manual will be provided to each researcher involved in the study, containing the definitions and steps to be followed to adequately fill in the data collected ISHION study.

Each site's lead researcher must record the number of oncological patients not eligible (admitted for <24h) or not meeting inclusion criteria and the reason for exclusion.

This can be easily recorded in the database if each researcher registers all consecutive.

Haemato-oncological patients admitted to PICU since their study start date (the actual date on which the first subject of each site has enrolled).

6.2 Inclusion criteria

The patients under study are all HO patients admitted for more than 1 day in the Paediatric Intensive Care Units during the control period. More than 1 day is considered when the difference between the dates of discharge minus the date of admission is greater than 24 hours.

6.3 Exclusion criteria

Those patients admitted before the study period and who remain admitted during the study phase will not be included in the study. Age < 30 days or infants with a corrected gestational age < 44 weeks, or age > 18 years.

7 Treatment and study visits

As this will be a prospective observational study, no further or different visit/examination/specific test will be carried out rather than those usual tests performed as if the patient would not participate.

The study will consist solely of prospectively data collection during routine follow-up visits, without the addition of study-specific scans or visits.

8 Study calendar

Data will be collected from January 2025 to December 2027. The analysis of the collected data will be done by the end of December 2025.

9 Data management

The ISHION study will be hosted in the REDCap database which is in the Computer Service of the Hospital Sant Joan de Déu and is accessed through a web page. The information and data are hosted on the corporate server, and each terminal only accesses the information.
The database consists of a set of tablets that are related to each other. To fill in the data in these tables, forms are used, which make the process more convenient. The program is equipped with an error control system and data confirmation. In addition, there are other tables containing various options (infections, antibiotics, etc.) that make it easier to fill in some aspects of the forms. Finally, other parts of the program are used to control possible errors (dates, diagnoses, etc. ....) or to confirm the data entered.

Each unit will have a researcher responsible for data entry and reliability. A password is required to access the web site. The data referring to the patient's history number and date of admission, once entered, are encrypted and stored in this way in the database. Only the physician who has entered the data can extract it again by decrypting the patient's identification data, which allows quality controls and analysis of the data entered.

The database provides the opportunity to full fill all following forms with each specific variable. ISHION study aims to coordinate and analyse data regarding hospital-acquired infection.

9.1 Data origin:

Researchers will access the database using a coding system obtained through a request to ISHION study coordinators (Iolanda Jordan and Carmina Guitart, HSJD).
The collected data is kept anonymous in the database through an encryption process of the medical record number and unit code. The patient's identity cannot be known except for the third researcher who will have registered the patient through the decryption process. In

accordance with the law 3/2018, the third person who accesses the medical record, collects the data, and assigns a code to which only they have access, cannot be part of the research team.

As a prospective non-interventional study, it is not subject to the ethical requirements of clinical trials.

It is considered that obtaining informed consent (IC) from each patient is not necessary. Article 58 of the Biomedical Research Law (14/2007) allows for the exemption from informed consent if the following requirements are met: obtaining IC is not possible or represents an unreasonable effort, it is research of general interest, the research is less effective or not possible without the identifying data of the source subject, there is no explicit objection from the subject, and the confidentiality of personal data is guaranteed.

Although the law refers to biological samples, it seems logical that these criteria should also be applied in cases of research with personal data, such as the ENVIN-HELICS registry.

The ISHION fulfils several of the mentioned criteria that support the idea that approval by the CEIC of each hospital does not require IC:

1. Patients and/or parents/guardians have signed the consent to use of data for research and the study does not involve any intervention other than usual practice.
2. Whether the patient or their family/tutors express their explicit opposition, data will not be registered.
3. Obtaining IC from over thousand patients every year is an unreasonable effort.
4. This research of general interest since the MSSSI has recognized ENVIN-HELICS as a Registry of Interest for the National Health System. The MSSSI itself participates in the funding of the registry through the funding of intervention projects.
5. The research is not possible without some identifying data of the source subject since it needs to specifically analyse risk factors and patient-related outcomes.
6. When the patient or their family expresses explicit objection, their data is not recorded.
7. Confidentiality of personal data is guaranteed.

For these reasons, it is considered that obtaining informed consent would not be necessary, although there may be an option for patients to express their refusal to have their personal data included in the study, in which case they should not be included.

9.2 Data Communication, Data Processors, and International Transfers.

Each PICU will designate an intensivist physician responsible for data entry, who will ensure the

reliability of their data. In general, the collaborating members are directly involved in the patient's treatment. Collaborators (both physicians and nurses) may be involved in data collection. These collaborators, together with the principal investigator of each PICU, are included in the annual reports. The coordinating team will elaborate a certificate of participation in ISHION study when required by the investigators of each hospital or their collaborators.

The coordinating team is currently (year 2024) composed by:

- Carmina Guitart. Paediatric Intensive Care Unit. Sant Joan de Déu Hospital (Barcelona).
- Iolanda Jordan. Paediatric Intensive Care Unit. Sant Joan de Déu Hospital (Barcelona).

A face-to-face meeting of most of the researchers (about 20 people) will be held bi-annually. One meeting prior to the starting annual collection period and another by the end of the study period with data analysis results, concepts related to definitions and data entry reinforced, and any modifications update.

The analysis of general data or partial aspects of these data are made upon request to the coordinating group. The publication policy is governed by the rules of the SEMICYUC infectious diseases and sepsis study group.

In accordance with the seventeenth provision of Organic Law 3/2018 on the protection of personal data and the guarantee of digital rights, health data from medical records may only be used for research if a pseudonymisation procedure is carried out.

There will not be international data transfer out of EU countries.

10 Biological samples management

Not aplicable.

11 Statistics

11.1 Sample size

The principal investigators estimate a collection of around 400 patients each year.

11.2 Statistical analysis

The statistical analysis will be performed by the SPSS program.

Qualitative variables are described by the percentage distribution of each category. Quantitative variables are described by the mean and standard deviation when they follow a normal distribution; otherwise, the median is used. They have been analysed using analysis of variance (ANOVA).

The comparison of qualitative variables is expressed as a percentage of the different categories and analysed using the linear association test of the chi-square test ($\chi 2$). In the case of ordinal variables (age or categorized APACHE II), the student's t-test has been used. The accepted level of statistical significance has been set at 5% ($p < 0.05$).

The database is closed on December 15th of each current year to debug the data and perform the corresponding statistical analysis.

Frequency measures

- Incidence rates (IR) and incidence density (ID) have been used as frequency indicators for each of the controlled infections.
- The incidence rate, expressed as a percentage, includes in the numerator the absolute number of the analysed infection and in the denominator the total number of at-risk patients:
    - the total number of patients included in the study.
    - the total number of patients with the risk factor related to the infection.
- The incidence density of each analysed infection includes in the numerator the absolute number of the analysed infection and in the denominator:
    - the number of at-risk days for all admitted patients, per thousand.
    - the number of days with the presence of the risk factor related to each infection, per thousand.

Analysis by hospital size

Hospitals have been classified as large, medium, and small. Hospitals with more than 500 beds are considered large, those between 200 and 500 beds are medium-sized, and those with fewer than 200 beds are small. In each group, the rates of different controlled infections, microorganisms, and markers of multidrug resistance will be analysed.

12 Ethics and legal aspects

The study will be conducted in compliance with the Declaration of Helsinki (version in force; currently Fortaleza, Brazil, October 2013). The study will be carried out in accordance with the protocol and with the relevant legal requirements: the use of health data in research, the study will comply with Organic Law 3/2018, of December 5, on the protection of personal data and the guarantee of digital rights.

The consent will not be requested, so please find attached the completed consent exemption request and the data management commitment.

Researchers will access the database using a coding system obtained through a request to ISHION study coordinators. The collected data will be kept anonymous in the database through an encryption process of the medical record number and unit code. The patient's identity cannot be known except for the third researcher who will have registered the patient and through the decryption process. In accordance with the 3/2018 law, the third person who accesses the medical record, collects the data, and assigns a code to which only they have access, cannot be part of the research team. As a prospective non-interventional study, it is not subject to ethical requirements of clinical trials.

13 Data confidentiality

The coordinators of the study, Iolanda Jordan and Carmina Guitart will request a formal Non-disclosure Agreement with every research center, as follows:

1. Confidential information

The “ISHION” Research Project hereby confirms that it will disclose certain of its confidential and proprietary information to the researchers.

Confidential information shall include all data, specifications, and other information disclosed or submitted, orally, in writing, or by any other media, to the local investigators by the study principal investigators (Iolanda Jordan and Carmina Guitart)

2. Agreement

A. Confidential data for ISHION research study is to be used solely for the purposes of said study and other research follow-up research within the same research area along with the principal investigators (Iolanda Jordan and Carmina Guitart).

B. Local principal investigator agrees not to disclose, publish or otherwise reveal any of the

confidential information received from Iolanda Jordan or Carmina Guitart research assistants or other participants of the project to any other party whatsoever except with the specific prior written authorization of Iolanda Jordan and Carmina Guitart.

The processing, communication, and transfer of personal data of all participants will comply with EU Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons concerning the processing of personal data and the free movement of such data, effective from 25 May 2018, as well as with Organic Law 3/2018 of 5 December on the Protection of Personal Data and guarantee of digital rights. The legal basis for data processing is the patient's signed consent, as established in Article 9 of EU Regulation 2016/679.

The data collected in this study will be identified only by a code, and no information that could identify the participants will be included. Only the study physician and collaborators with the right to access source data (medical records) will be able to link the study data with the patient's medical history.

The identity of the participants will not be disclosed to anyone else, except in the case of a medical emergency or legal requirement. Access to identified personal information may be granted to health authorities, the Research Ethics Committee (CEIm), and authorized personnel of the study sponsor when necessary to verify study data and procedures. However, confidentiality will always be maintained in accordance with applicable legislation.

Only coded data will be transferred to third parties and other countries, and this data will not contain any information that could directly identify the participant (such as name, initials, address, social security number, date of birth, etc.). If any transfer occurs, it will be for the same purpose as the described study and with guaranteed confidentiality.

If a transfer of coded data outside the EU is necessary, whether to entities related to the hospital where the patient is participating, to service providers, or to researchers collaborating with us, participant data will be protected by safeguards such as contracts or other mechanisms established by data protection authorities.

As project sponsors, we commit to processing data in accordance with EU Regulation 2016/679, including maintaining a record of processing activities, conducting a risk assessment for the data processing we perform, and determining appropriate protective measures.

The investigator and sponsor will retain the data collected for the study for at least 10 years after its conclusion. After this period, personal information will only be retained by the hospital for patient care and by the sponsor for other scientific research purposes, provided the patient has given consent and if permitted by law and ethical requirements.

14 Finance

None of the researchers, collaborators, or members of the coordinating group receives fees for participating in the ISHION study.

15 Publications politics

Researchers commit on sharing and publishing the results whether they are positive or negative.