Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità BANDO RICERCA FINALIZZATA 2021 esercizio finanziario anni 2020-2021 - Progetto Completo	**Project Title:** ACUTE project: Adapting blood CUlture systems To monitor antimicrobial Efficacy **Project duration (months):** 36
Project Code:	**Principal Investigator:** Zaghi Irene
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Emilia-Romagna

Project Type: Starting grant

MDC primary: Diagnostica

MDC secondary: Malattie Infettive

Project Classification IRG: Infectious Diseases and Microbiology

Project Classification SS: Clinical Research and Field Studies of Infectious Diseases - CRFS

Project Keyword 1: Design and execution of investigator-initiated clinical studies for testing agents or strategies for preventing or treating infectious diseases

Project Keyword 2: pharmacodynamic marker

Project Keyword 3: MDR Gram negative pathogens

Project Request: **Animals:** ☐ **Humans:** ☒ **Clinical trial:** ☒

The object/s of this application is/are under patent copyright Y/N: ☐

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Overall Summary

Bacterial sepsis is a leading cause of death in intensive care units (ICUs) with one-third of patients never receiving timely adequate antimicrobial therapy. This project will utilize automatic blood culture systems already available in clinical microbiology laboratories to develop a validated Time-to-positivity (Tpos) assay for measuring bactericidal activity of patient¿s serum. Our hypothesis is that the time taken for a standardized bacterial inoculum to "grow through" the antimicrobial effect provided by the patient's serum sample collected during antibiotic treatment can serve as a surrogate pharmacodynamic index for predicting antibiotic efficacy. Hence, a short Tpos (i.e. < 10 hours) would provide an early indication that a patient is receiving an inadequate antimicrobial treatment regimen and should prompt therapy modification to improve patient outcome.

Background / State of Art

Several medical societies recommend individualized antibiotic dosing approaches for patients who are critically ill that rely on: i) improving antibiotic PK/PD performance through enhanced dosing techniques (e.g., continuous infusion of ß-lactams); ii) therapeutic drug monitoring (TDM) of serum antibiotic concentrations; and iii) Bayesian-forecasted computer dose-adjustment using the patient's TDM and microbiology results. However, this approach is both resource and time-intensive. Moreover, the predictive performance of computer-forecasted dose adjustment depends on the population PK models used for Bayesian priors, which may not be directly applicable to the patient being treated, nor account for effects of combination antibiotic therapy. In contrast, measurement of Tpos provides a direct indication of bactericidal activity in the patient¿s serum during antibiotic therapy, and is directly impacted by patient pharmacokinetics, antibiotic pharmacodynamics (including in vivo synergistic or antagonistic interactions for combination therapy), and pathogen susceptibility. Serum bactericidal test is the other method to ex vivo monitoring antimicrobial activity in blood, but remains cumbersome and with long turnaround time for results. The advantage of a validated Tpos assay is that it could likely provide actionable results within 12 hours that are easy to interpret and report by any clinical microbiology laboratory.

It’s available a Systematic Review on this topic? No

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Hyphotesis and Specific AIMS

Hyphotesis and Significance

Our central hypothesis is that a short Tpos (i.e. < 11 hours) can be developed as a reliable surrogate marker for poor bactericidal activity in patient serum during antibiotic therapy of gram-negative infections.

Preliminary Data

Since the early days of antibiotic therapy, the need for optimization and monitoring of antimicrobial efficacy has been evident. Serum bactericidal test (SBT) is one of the few ex-vivo assays that permit monitoring of antimicrobial efficacy. However, despite its wide use in the past, it remains time-consuming, requires dedicated laboratory personnel and has low inter-laboratory reproducibility.

In 2005, a research group led by Prof. Jon Cohen, M.D., Brighton and Sussex Medical School, UK, first proposed a simple and rapid approach for measuring SBT-like endpoints by analysing the time-to-positivity (Tpos) in an automated blood culture detection system (e.g., BacT/ALERT, Biomérieux Inc)[1]. The assay measures the time taken for the standardised bacterial inoculum to "grow through" antimicrobial activity present in the patient¿s serum under defined conditions. Therefore, a short Tpos would indicate inadequate antimicrobial activity, and theoretically could predict worse clinical outcome.

The authors subsequently demonstrated that (i) Tpos correlates directly with antimicrobial concentrations (pharmacokinetics) and antibacterial activity in patient serum and (ii) considerable variability was observed in Tpos results from ICU patients receiving the same antibiotic regimens, thus paralleling the wide variations in ß-lactam exposures reported in previous pharmacokinetic point-prevalence studies.

In a follow-up prospective non-interventional study from the same UK research group, Tpos was measured in 48 adult patients with sepsis within 24 hours (Tpos1) or at 72 hours (Tpos2) after starting antimicrobial therapy[2]. The serum was tested using a representative "indicator" organism based on the empirical antibacterial therapy administered (i.e., methicillin-sensitive S. aureus, methicillin-resistant S. aureus, E. coli or P. aeruginosa). Patients with a Tpos1 result shorter than 10 hrs (indicative of inadequate antimicrobial therapy) had significantly longer duration of ICU hospitalization versus patients with adequate (> 10 hrs) Tpos1 results (14.4 vs. 7.8 days, P=0.028). Even after adjustment for severity of illness, the median length of hospital stay in patients with inadequate Tpos1 was significantly longer than patients with an initially adequate Tpos1 results (31 days vs. 13 days; p=0.001)

They therefore demonstrated that Tpos performed with "indicator" organisms-i.e. reference isolates representative of typical ICU pathogens, provided results in less than 12 hours that correlated with duration of ICU and hospital stay of patients, even after adjustment for patient severity of illness; however, their studies did not include MDR isolates. These background data indicate that Tpos could be developed as a rapid surrogate biomarker of antimicrobial serum PK/PD in patients receiving antibiotic therapy for BSI caused by difficult-to-treat pathogens.

This proposal will build upon the previous work by Kaltsas and Jerwood but advance the development and validation of Tpos further by: i) focusing on the in vitro validation of the test for KPC-K. pneumoniae treated with ceftazidime/avibactam, CR P. aeruginosa treated with ceftolozane/tazobactam and single-regimen therapies and combinations for A. baumannii including XDR isolates, ii) using pharmacometric models, we will explore the correlation of Tpos results with ceftazidime-avibactam, ceftolozane/tazobactam and cefiderocol PK/PD exposures (e.g., free plasma ceftazidime > 8 mg/L; avibactam 1 mg/L for ¿ 50% of dosing interval, %fT>MIC, Cmin/MIC) in critically-ill patients undergoing treatment for KPC-Kp BSI, CR P. aeruginosa and CR A. baumannii, iii) validating the assay for A. baumannii XDR isolates, we will explore how Tpos predict synergistic or antagonistic effect of combination therapies.

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Picture to support preliminary data
preliminary data.jpg

Specific Aim 1

(In vitro studies, 6-12 months): To validate the direct quantitative relationship between Tpos and viable gram-negative bacteria in blood culture alone, following single-regimen antibiotic exposure and combination therapies. To develop models and perform simulations of how variability in antimicrobial PK/PD targets will impact Tpos results and examine optimal sampling schemes.

Specific Aim 2

(18-24 months): pilot observational clinical study in 70 patients undergoing treatment with ceftazidime /avibactam for KPC-Klebsiella pneumoniae BSI, to explore how early Tpos results performed with indicator test isolates compare to results performed with the patient's isolate. We will also correlate Tpos results with individual patient PK/PD exposures.

Specific Aim 3

(in vitro studies, 6 months) To describe how Tpos is affected by commonly used antibiotic combinations. Combination therapy is routinely recommended for MDR-resistant Gram-negative pathogens, particularly P. aeruginosa and Acinetobacter baumannii (ref IDSA and ESCMID guidelines).

Experimental Design Aim 1

i) Establishing the quantitative relationship of Tpos and bacterial inoculum in blood culture: tubes containing 1.8 mL of pooled healthy human serum will be inoculated with 0.2 mL of a series of seven ten-fold dilutions (5x101 to 5x107 CFU/mL) of the standardized inoculum of each test indicator strains (Klebsiella pneumoniae ATCC 700721 reference strain- negative control or test indicator organism as carbapenem susceptible; Klebsiella pneumonia ST512 (blaKPC-2, blaSHV) and Klebsiella pneumonia ST512 (blaKPC-3, blaSHV) as carbapenem-resistant; Klebsiella pneumonia ST1519 (blaKPC-3 with D179Y mutation)- "positive control" as carbapenem-resistant, ceftazidime/avibactam resistant). The inoculated sera are then transferred into BacT-ALERT bottles without inactivating matrix (Biomérieux Inc) for aerobic incubation and monitored for time to positivity. Tpos results will be used to establish preliminary assay quality control ranges and confirm the utility of isolates as selected ¿indicator¿ organisms and quality control ranges at specific inoculum thresholds. Experiments will be performed in at least 10 replicates. The main goal of this work package is to demonstrate that Tpos results under the assay conditions exhibit a reproducible and reliable relationship with bacterial inoculum for representative KPC-carbapenemase-producing strains of Klebsiella pneumoniae.
ii) to describe how antibiotic concentrations impact Tpos. To define the relationship between Tpos and ceftazidime-avibactam concentrations, tubes containing 1 mL of normal human serum and 10 antibiotic concentrations (covering the normal therapeutic range and concentrations below and above the MIC) will be inoculated with 1 mL of Mueller-Hinton (MH) broth containing 0.5x106 or 1x106CFU for each concentration-bacterium pair, and then transferred to BacT ALERT bottles for aerobic incubation. The experiments will be performed in 5 replicates. The relationship between antibiotic concentrations, Tpos and concentrations/MIC will then be analyzed using linear and non-linear models using the drc package (R Core Team-2021 R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) to summarize concentration-effect relationships with Tpos. The same experiments will be performed for n=5 P. aeruginosa isolates and 5 Acinetobacter baumannii isolates (reference wild-type and carbapenem-resistant isolates representing common carbapenemase mechanisms) treated with ceftolozane-tazobactam.

iii) Using published population PK models for ceftazidime-avibactam and ceftolozane-tazobactam and exposure-response relationships identified in Aim 1 and reported in the literature[3-5], we will simulate and predict how variations in ceftazidime-avibactam and ceftolozane-tazobactam exposure or isolate MICs will impact Tpos at various timepoints and explore optimal sampling times for Tpos monitoring. Analysis will be performed using nonlinear mixed-effect modeling in R using the nlmixr and rxODE and PFIM 4.0 packages[6]. Part of Aim 1 Workpackage 1C (3 months) will be performed in collaboration with BTCCRC (Burns Trauma and Critical Care Research Centre, School of Medicine, Royal Brisbane and Women's Hospital, The University of Queensland, Australia); the PI has won an observership grant by the European group of Infectious Diseases that will cover partial travel costs and that will require a report on the objects and results achieved by the PI during the observership.

Experimental Design Aim 2

Eligible patients will be prospectively screened from blood culture reports from the Unit of Microbiology (UoM) Great Romagna Hub laboratory, located in Pievesestina (FC), Italy, which serves a network of 14 hospitals with a total of more than 4400 beds. In this network, 7 ICUs are included with some 100 beds. Serum (7 mL) from a 15 mL blood samples collected at the time of follow-up blood cultures or samples for TDM will be separated and inoculated (1mL per bottle-3 bottles) into one BacT-ALERT alert bottle containing one of two ¿indicator¿ organisms (0.5x106 or 1x106CFU) and one BacT/ALERT bottle containing the patient isolate (0.5x106 or 1x106CFU) to determine Tpos. An aliquot of the serum will be submitted for analysis of antibiotic concentrations by validated LC/MS/MS. Remaining aliquots of serum will be banked for potentially further analysis if needed.
For each enrolled patient, we will collect data on serum creatinine (for CrCL calculations), presence of augmented renal clearance and full information on antibiotic dosing and plasma sampling. We will also collect data on infection status (i.e. copresence of pneumonia, ventilator-associated pneumonia, complicated intraabdominal infection, etc.), markers of systemic disturbances e.g., white blood cell (WBC) count ¿ 12,000/¿L, presence of fever, systemic inflammatory response syndrome or bacteremia, Acute Physiology and Chronic Health Evaluation version II, sequential organ failure assessment score (SOFA score), sex, age, obesity status and body weight, race, end-stage renal disease or dialysis, mechanical ventilation and receipt of pressors.
The population PK model and serum drug concentration analysis results will be used to derive Bayes estimates of individual PK parameters for all study subjects (e.g., maximum plasma concentration at steady state (Cmax,ss) and area under the plasma concentration-time curve at steady-state (AUCss,0-24). Blood concentration-time courses of ceftazidime and avibactam, ceftolozane and tazobactam, ampicillin-sulbactam etc will then be simulated for all patients using observed CrCL taken closest to the Tpos sampling.
A joint PK/PD target for ceftazidime and avibactam will be used to assess the suitability of ceftazidime/avibactam dosing. Our initial analysis will focus on simultaneous achievement of 50% time (during each dosing interval) free plasma concentrations exceed ceftazidime-avibactam minimal inhibitory concentration (MIC) of 8 mg/L for ceftazidime (50% fT > 8 mg/L) and 50% fT above a threshold concentration (CT) of 1 mg/L for avibactam (50% fT > 1 mg/L) as previously described[3]. The relationship of these targets and Tpos will then be compared to assess candidate ¿cut-offs¿ for interpretation of Tpos based on proposed PK/PD breakpoints.

Experimental Design Aim 3

Antimicrobial combinations are rarely tested in clinical microbiology laboratories, making selection of which combinations to use largely empiric or based on individual susceptibility profiles. SBTs are one of the few laboratory tests that have been used to identify/confirm synergistic bactericidal activity in patients, such as the use of early anti-pseudomonal penicillins with aminoglycosides in the treatment of Gram-negative bloodstream infections during neutropenic fever. However, the SBT

remains cumbersome to perform and results may not be reported in a timely fashion. Because Tpos results are directly related to SBT, changes in Tpos with mono versus combination therapy or changes in the distribution of Tpos with common combinations may provide a facile marker for antimicrobial synergy for MDR pathogens. In this specific aim we will construct 8x8 arrays of Tpos bottles covering a range of clinically-achievable drug concentrations.

Metodologies and statistical analyses:

Methodologies (describe all measures taken to minimize / avoid bias)
We will follow the classic learn, predict, confirm model [7] to examine the utility of Tpos as a surrogate pharmacodynamic biomarker for assessing antimicrobial efficacy. All analysis will follow principles of transparency to produce reproducible and explainable models to encourage third-party auditing or adjustments. Our goal is to allow any investigator who is willing to review the R source code to reproduce our modeling and data analysis. Therefore our workflow will exclusively use analysis tools from the ¿R¿ ecosystem to produce scripted, literate-programming analysis, reports and figures using open-source R packages (e.g., nlmixr instead of NONMEM)[8,9]. Deidentified data sets will be provided with the code on a Github-hosted repository, and population PK/PD models for Tpos interpretation will be ported to web applications (Shinyapps) to allow investigators unfamiliar to R programming to interact and test the models

Methods of data collection (Indicate the data that will be collected, the tools used)
We will collect data on the quantitative relationship of Tpos and bacterial inoculum in blood culture and how the presence of antibiotic at concentrations covering the therapeutic concentration affect Tpos results. The relationship between antibiotic concentrations, Tpos and concentrations/MIC will be analyzed using linear and non-linear models using the drc package (R Core Team-2021 R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) to summarize concentration-effect relationships with Tpos. To draw models based on the exposure-response relationships identified in Aim 1 and the published PK/PD models, we will use nonlinear mixed-effect modeling in R using the nlmixr and rxODE and PFIM 4.0 packages.

Statistic plan (calculation of statistical data)
The project will be divided into Specific Aim 1 which includes Workpackages 1A and 1B which will determine the quantitative relationship of Tpos results and bacterial load and how they are affected by antibiotic concentrations. Analysis of these data will permit to draw simulations, create PK/PD models and optimal sampling schemes (Workpackage 1C) to be applied in Specific Aim 2. Specific Aim 3 wi run in parallel and will analyze in vitro the effect of combination therapies on Tpos results (we will focus on MDR resistant Gram-negative pathogens, particularly P. aeruginosa and Acinetobacter baumannii, for which combination therapy is recommended by IDSA and ESCMID guidelines. See Gantt chart.

Statistical analysis (describe the main statistical analysis)
The relationship between antibiotic concentrations, Tpos and concentrations/MIC will be analyzed using linear and non-linear models using the drc package (R Core Team-2021 R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) to summarize concentration-effect relationships with Tpos. To draw models based on the exposure-response relationships identified in Aim 1 and the published PK/PD models, we will use nonlinear mixed-effect modeling in R using the nlmixr and rxODE and PFIM 4.0 packages.

Timing of analysis data (indicate duration of study: duration of enrollment, of therapy, follow-up etc)

Specific aim 1 and 3 encompass the in vitro section and will cover the first 18 months of the project; we expect to have the microbiological and pharmacological data (relationship between antibiotic concentrations, Tpos and concentrations/MIC, how variations in ceftazidime-avibactam and ceftolozane-tazobactam exposure or isolate MICs impact Tpos at various timepoints, optimal sampling times for Tpos monitoring) available before specific aim 2 is started. Based on the number of inpatients admitted in the ICU department of Area Vasta Romagna, we think that enrolment of 70 patients (20 patients with KPC bacteremia, 20 patients with CR P. aeruginosa bacteremia and 30 patients with CR A. baumannii bacteremia) will be feasible over a period of 18-24 months. Enrollment can be started while specific Aim 3 is still ongoing, and clinical data and samples banked for later analysis to derive Bayes estimates of individual PK parameters.

Expected outcomes

We anticipate data from this project will demonstrate: i) the quantitative relationship between bacterial CFU/mL and Tpos in automated blood culture detection systems; ii) the quantitative relationship between the selected antibiotic concentrations and Tpos in automated blood culture detection systems; iii) the quantitative relationship between individual PK/PD target attainment and Tpos in critically-ill patients receiving ceftazidime-avibactam therapy for KPC-Kp BSI; iv) effect of combination therapies on Tpos results highlighting synergistic or antagonistic effect. The results of this study will serve as a proof of concept and form the basis for further investigations with other novel antibiotics. We also believe our data could provide guidance to determine how Tpos may be best employed clinically- i.e. as an early screening surrogate marker to identify patients with subtherapeutic drug exposures who are candidates for more intensive TDM/dosing adjustment, or as a monitoring tool for using the patient¿s isolate, especially if they are transitioned to narrower-spectrum or oral therapy. Hence the broader development and validation of Tpos could serve as an important complementary laboratory test for supporting antimicrobial stewardship.

Risk analysis, possible problems and solutions

Aims 1 encompasses in vitro work that builds upon previously published studies by Kaltsas[1] and Jerwood[2]. Given the extensively and reproducibly demonstrated quantitative relationship of both Gram-positive and Gram-negative bacterial inocula with Tpos reported in the diagnostic and clinical studies, we do not anticipate major technical hurdles in these work packages that cannot be overcome by substituting isolates and modifying assay conditions. The modeling of pharmacodynamic relationships between ceftazidime-avibactam and KPC-Kp CFU/mL has been addressed by several previous investigators (e.g., Sy et al.[10]) that can be similarly explored using approaches with Tpos.
Specific Aim 2: We believe enrolment of 70 patients is feasible based on the number of inpatients (4400) and ICU (100) beds served by the reference UoM microbiology unit where this study will be performed. On average the unit processes over 100 KPC- Klebsiella pneumoniae, 250 CR A. baumannii and 100 CR P. aeruginosa bloodstream isolates annually. Although combination therapy is not promoted, we cannot exclude that a significant number of patients may receive additional 2nd and 3rd line antibiotics. This will not be initially considered as an exclusion criterion for enrolment but samples may be banked for later analysis only if a sufficient number of patients receiving monotherapy cannot be enrolled. It is possible to repeat experiments in Specific Aim 1 and 2 to look at the specific effects of the combination agent (e.g., gentamicin) on Tpos to assess possible synergistic or antagonistic interactions and potentially account for this effect in subsequent analysis. Another possible challenge is that the vast majority of ceftazidime-avibactam-treated patients enrolled in the study will achieve high PK/PD exposures with prolonged Tpos, thus limiting the breadth/resolution of exposures that would be required to fully describe a relationship between Tpos and PK/PD targets. Although this has been predicted by some population PK modeling using phase III patient data[3], our region has observed clinical failures with the emergence

of resistance in patients with KPC-Kp BSI treated with ceftazidime-avibactam monotherapy[11], as well as subtherapeutic exposures in patients with augmented renal clearance and high-volume dialysis[12]. A possible solution to address this issue would be to retest banked serum aliquots from patients against additional KPC-Kp isolates with higher MICs to create a wider range of Tpos and PK/PD exposures pending follow-up further studies enrolling patients with more resistant pathogens or altered pharmacokinetics.

Significance and Innovation

The need to individualize and improve antibiotic therapy selection/dosing for patients with gram-negative sepsis is an urgent and largely unmet medical need. The development and validation of the Tpos assay would provide microbiology laboratories and clinicians with a rapid (< 12 hours) direct measure of bactericidal activity in the patient serum during antibiotic treatment that could indicate if the patient is receiving suboptimal antimicrobial therapy. Beyond direct patient care, Tpos could provide an important surrogate endpoint for clinical studies of antibiotic treatment and resistance, particularly for studies exploring novel antibiotics/ dosing regimens for the treatment of MDR pathogens or populations with potentially altered PK/PD (e.g., immunocompromised, liver cirrhosis, pregnancy, pediatrics). We previously proposed 10 novel clinical and epidemiological study designs that could incorporate validated PD surrogate endpoints such as Tpos[13].

Training and tutorial activities

During the project, the PI will have the opportunity to integrate experience in the clinical field of infectious diseases with laboratory activity and validation of the test to be applied in the clinical context. Workpackage C1 is specifically pharmacological-based and part of it will be performed at BTCCRC (Burns, Trauma and Critical Care Research Centre), current leading international group of clinical pharmacology of antibiotics, as part of an ESCMID-funded observership programme. The project has been granted by ESCMID (European Society of Clinical Microbiology and Infectious Diseases) as part of the ESCMID research grant programme 2022 with a benefit of 20.000 euros to cover 24 months with a final report and auspicable publication with CMI (Clinical Microbiology and Infection).

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Project Type: Starting grant

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12.Gatti M et al. Antimicrobial Dose Reduction in Continuous Renal Replacement Therapy: Myth or Real Need? A Practical Approach for Guiding Dose Optimization of Novel Antibiotics
13.Zaghi I et al. Serum bactericidal titres for monitoring antimicrobial therapy: current status and potential role in the management of multidrug-resistant Gram-negative infections
14.Cohen J et al. Sepsis: a roadmap for future research

Timeline / Deliverables / Payable Milestones

The project will develop into three main sections: specific aim 1 and 3 will cover the first 18 months; they will focus on the in vitro validation of Tpos assay, exploring how bacterial load and antibiotic concentration (as single-regimen or combinations) wil affect Tpos results. After the first in vitro results are available Workpackage 1C will generate PK/PD models and simulations on how variability in antimicrobial PK/PD targets will impact Tpos results and examine optimal sampling schemes to be used in Aim 2. Aim 1 and 3 will cover the largest amount of the budget in terms of supplies, IT services and database and travel expenses. Aim 2 will cover the last 18 months of the project in the form of pilot observational clinical study managed by the PI; we expect to utilise the budget for database and data elaboration, publications and congress attendance to present our results.

Milestones 18 month

we expect to have the assay's in vitro validation completed; we will establish quantitative reproducible relationship between Tpos-bacterial inoculum and between Tpos-serial antibiotic concentrations and combinations, with predictions on how antibiotic or isolate MIC variations will impact Tpos at various timepoints. We expect to have Tpos cutoffs identified

representing inadequate antimicrobial activity against the representative bacteria and the optimal sampling schemes to be applied in Aim 2

Milestones 36 month

we expect to know the quantitative relationship between individual PK/PD target attainment, TDMs and Tpos in critically-ill patients, with analysis of how Tpos performs with patient¿s isolate compared to the referral strain. In case of combination therapies, we will explore the impact on Tpos results, investigating synergistic or antagonistic interactions in vivo. It will be defined how Tpos can be used as a valid and reliable surrogate pharmacodynamic index of antimicrobial efficacy

Gantt chart

Gantt chart RF.png

Equipment and resources available

Facilities Available

The Unit of Microbiology (UoM) ¿ DIMES, The Great Romagna Hub laboratory serves a network of 14 hospital swith a total of more than 4400 beds. In this network, 7 ICUs are included with some 100 beds. The UoM has 82 staff with 45 members dedicated to bacteriology workflows with several BacT/ALERT that could be devoted to completion of the project. The laboratory is located in Pievesestina (FC), Italy. The UoM has full facilities for bacterial growth and identification, including smart incubators for plate imaging and analysis: this is supported by an AI software for the calculation of the mortality risk for septic patients that enables the best use of the diagnostic resources (in a personalized way according to the overall clinical risk of each individual patient). Of course the UoM has full microscopy analysis capability and many automated (and manual) systems for the performing of Antimicrobial Susceptibility Testing (from Vitek and Microscan to E-test and broth microdilution). As far as the BC system is concerned, the UoM has available for current work a complete bioMerieux VIRTUO system for a total number of more than 800 incubation position. A full set of molecular biology diagnostic system are also available.

Subcontract

non included in SG projects

Translational relevance and impact for the National Health System (SSN)

This project will provide cornerstone microbiology and clinical data supporting the development and validation of Tpos as a simple, rapid tool for monitoring antibiotic therapy of gram-negative infections. The performance and clinical utility of the test can then be confirmed in larger, multicentre validation studies, and eventually randomized trials in patients with gram-negative sepsis[14]. Specifically, the test addresses key priorities in sepsis of developing new monitoring tools for personalized medicine and strategies for ensuring patients are administered the right antibiotic, at the right dose, in a timely fashion.

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PRINCIPAL INVESTIGATOR PROFILE

Zaghi Irene

Birth date: 28/05/1992

Institution: U.O. Microbiologia AUSL Romagna

Department/Unit: Centro Servizi Pievesestina, U.O. Microbiologia AUSL Romagna, Piazza della Liberazione, 60 47522 Cesena

Position Title: Laureato frequentatore

Education/Training - Institution and Location	Degree	Year(s)	Field of study
Medical specialization in Infectious and Tropical Diseases, University of Bologna, Sant'Orsola-Malpighi hospital	Specialization in Infectious and Tropical Diseases	2022	Infectious and Tropical diseases
University of Medicine and Surgery, Alma Mater Studiorum, University of Bologna, Italy	Degree in Medicine and Surgery	2016	Medicine and Surgery

Personal Statement

Main goal of the project is to validate Tpos assay as an alternative, rapid and cheap method that permits to measure bactericidal activity of patient¿s serum. As a surrogate pharmacodynamic marker of antimicrobial efficacy ex vivo it can be used as a complementary tool to optimise antimicrobial dosing in populations with potentially altered PK/PD. It could provide an important surrogate endpoint for clinical studies of antibiotic treatment and resistance, exploring potential synergistic effect of combination therapies. The PI will be responsible of validating the test in vitro for MDR Gram negative infections, correlating Tpos results to PK/PD models and analysing how it performs in clinical practise in a pilot observational study involving patients treated for MDR Gram negative bacteremia.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Bologna, IRCCS Sant'orsola-Malpighi hospital, via massarenti 9, 40138, Bologna, italy	Covid department, Infectious diseases	Sant'orsola-Malpighi hospital, via massarenti 9, 40138, Bologna, italy	Medical doctor	2021	2022
Sant'Orsola-Malpighi hospital, Bologna, Italy	Infectious diseases department	Sant'Orsola-Malpighi, via Massarenti 9, 40138 Bologna, Italy	Resident in Infectious and Tropical diseases	2017	2022
Unit of Microbiology, The Great Romagna Hub Laboratory, Pievesestina (FC); DIMES, University of Bologna, Italy	Unit of Microbiology, Director Professor Vittorio Sambri	Pievesestina (FC), Piazza della Liberazione, 60 47522 Cesena, Italy	graduate frequenter	2022	2022

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità BANDO RICERCA FINALIZZATA 2021 esercizio finanziario anni 2020-2021 - Progetto Completo	**Project Title:** ACUTE project: Adapting blood CUlture systems To monitor antimicrobial Efficacy **Project duration (months):** 36
Project Code:	**Principal Investigator:** Zaghi Irene
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Emilia-Romagna

Project Type: Starting grant

Official H index: 2.0 (autocertificated)

Scopus Author Id:57210950164 **ORCID ID:**0000-0003-0687-9493 **RESEARCH ID:**AAD-6571-2022

Other awards and honors

the ACUTE project has been granted by the ESCMID (European Society of Infectious diseases and clinical microbiology) research grant 2022 (average acceptance rate 8-25%); moreover, the PI has won an ESCMID observership program to attend at the BTCCRC Department of clinical pharmacology, Brisbane, Australia, to focus of PK/PD models development and optimization strategies of antimicrobial therapy to be applied in the course of the project.

Other CV informations

November 2019: attendance at Comsaude referral center, AIFO in Tocantins, Brasil for the diagnosis of leprosy
August-October 2017: attendance at the dermatology unit in Ayder hospital, Mekellè, Ethiopia and ALERT hospital, Addis Abeba, Ethiopia
July-August 2017: collaboration with Professor Aldo Morrone (San Gallicano Hospital, Rome), in Tigray, Ethiopia, in a campaign of dermatological visits.
February-June 2017: attendance at the bacteriology unit, microbiology department, Sant¿orsola hospital, Bologna
June-Ocober 2016: attendance at the microbiology laboratory Centre Pasteur of Yaoundè, Cameroun

Mother language: Italian; other languages: English and french C1, Hebrew A1

Selected peer-reviewed publications of the PI valid for minimum expertise level

Title	Type	Pag	Vol	Year	DOI	PMID	IF	Cit.**	P.*
Serum bactericidal titres for monitoring antimicrobial therapy: current status and potential role in the management of multidrug-resistant Gram-negative infections	Review	1338-1344	26	2020	https://doi.org/10.1016/j.cmi.2020.04.036	32376295	1.0	3	F

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

Selected peer-reviewed publications of the PI for the evaluation CV

Title	Type	Pag	Vol	Year	DOI	PMID	IF	Cit.**	P.*
Reactivation of occult HBV infection in HIV treated for HCV: A retrospective study	meeting abstract	E256-E257	70	2019	10.1016/S0618-8278(19)30485-2		0.0	0	
IS INTRAPLEURAL FIBRINOLYTIC INSTILLATION THE RIGHT CHOICE FOR MULTI-SENSITIVE MYCOBACTERIUM TUBERCULOSIS COMPLEX AFFECTED PATIENTS? A CASE REPORT	poster at CHEST congress	104A-104A	157	2020	10.1016/j.chest.2020.05.115		0.0	0	

Project Title:
ACUTE project: Adapting blood CUlture systems To monitor antimicrobial Efficacy

Project duration (months): 36

Project Code:

Principal Investigator: Zaghi Irene

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Emilia-Romagna

Project Type: Starting grant

Title	Type	Pag	Vol	Year	DOI	PMID	IF	Cit.**	P.*
Serum bactericidal titres for monitoring antimicrobial therapy: current status and potential role in the management of multidrug-resistant Gram-negative infections	Review	1338-1344	26	2020	https://doi.org/10.1016/j.cmi.2020.04.036	32376295	1.0	1	
Autochthonous Cases of Mucosal Leishmaniasis in Northeastern Italy: Clinical Management and Novel Treatment Approaches	Article	588	8	2020	doi:10.3390/microorganisms8040588	32325735	1.0	1	
Factors associated with vitamin D deficiency in HIV-1 infected patients on combination antiretroviral therapy: a case-control study	Article	145-149	42	2019	New Microbiol. 2019 Jul;42(3):145-149. Epub 2019 Jul 15	31305932	1.0	1	

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

Employment contract extension:

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **BANDO RICERCA FINALIZZATA 2021** **esercizio finanziario anni 2020-2021 - Progetto Completo**	**Project Title:** ACUTE project: Adapting blood CUlture systems To monitor antimicrobial Efficacy **Project duration (months):** 36
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Project Type: Starting grant

Expertise Research Collaborators

** Autocertificated

Total proposed budget (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1b Researchers' Contracts	90.000,00	0,00	90.000,00	69,23
2 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a Supplies	20.000,00	0,00	20.000,00	15,38
3b Model Costs	600,00	0,00	600,00	0,46
3c Subcontracts *	0,00	0,00	0,00	0,00
3d Patient Costs	0,00	0,00	0,00	0,00
4 IT Services and Data Bases	9.000,00	0,00	9.000,00	6,92
5 Publication Costs	6.500,00	0,00	6.500,00	5,00
6 Convegni	1.300,00	0,00	1.300,00	1,00
7 Travels	2.600,00	0,00	2.600,00	2,00
Total	130.000,00	0,00	130.000,00	100,00

* percentage calculated as average value between all the Operating Units.

Report the Co-Funding Contributor:

not included

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **BANDO RICERCA FINALIZZATA 2021** **esercizio finanziario anni 2020-2021 - Progetto Completo**	**Project Title:** ACUTE project: Adapting blood CUlture systems To monitor antimicrobial Efficacy **Project duration (months):** 36
Project Code:	**Principal Investigator:** Zaghi Irene
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Emilia-Romagna

Project Type: Starting grant

Budget Justification	
1b Researchers' Contracts	90.000 euro for the PI contract
2 Equipment (Leasing - Rent)	0.00 euro requested: institution of Pievesisitna will provide all the machinery necessary for the project
3a Supplies	20.000 euro for materials and disposables
3b Model Costs	600 euro
3c Subcontracts	no subcontracts included for SG projects
3d Patient Costs	no patient costs expected
4 IT Services and Data Bases	9.000 euro are expected to be required for database and data analysis and elaboration
5 Publication Costs	he project has been granted by ESCMID research grant program and requires publication with CMI
6 Convegni	the first partial results of in vitro studies will be presented at the next ECCMID conference (European congress of Infectious diseases and clinical microbiology) and SIMIT.
7 Travels	Part of the project will be performed in conjuction with BTCCRC center (Queensland University, Brisbane, Australia) supervised by Prof. J. Roberts; the PI has won an ESCMID observership programme which will partially cover travel expenses

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **BANDO RICERCA FINALIZZATA 2021** **esercizio finanziario anni 2020-2021 - Progetto Completo**	**Project Title:** ACUTE project: Adapting blood CUlture systems To monitor antimicrobial Efficacy **Project duration (months):** 36
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Project Type: Starting grant

Principal Investigator Data

Cognome: Zaghi
Nome: Irene
Codice fiscale: ZGHRNI92E68A944A
Documento: Carta d'identità, Numero: ca79676du
Data di nascita: 28/05/1992
Luogo di nascita: Bologna
Provincia di nascita: BO
Indirizzo lavorativo: Piazza della Liberazione, 60 47522 Cesena
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CAP: 47522
Provincia: FC
Email: irene.zaghi@gmail.com
Altra email: irene.zaghi@studio.unibo.it
Telefono: +393396417020
Qualifica: Laureato frequentatore
Struttura: Centro Servizi Pievesestina, U.O. Microbiologia AUSL Romagna, Piazza della Liberazione, 60 47522 Cesena
Istituzione: U.O. Microbiologia AUSL Romagna
Datore/ente di lavoro? Si
Datore/ente di lavoro SSN? Si
Nome datore/ente di lavoro non SSN:
Nome istituzione SSN: U.O. Microbiologia AUSL Romagna Centro Servizi Pievesistina
Tipo contratto: Altro

Con l'invio della presente proposta si dichiara che la stessa o parti significative di essa non sono oggetto di altri finanziamenti pubblici o privati e che di conseguenza vi è assenza del c.d. doppio finanziamento ai sensi dell'art. 9 del Regolamento (UE) 2021/241, ossia che non ci sia una duplicazione del finanziamento degli stessi costi da parte di altri programmi dell'Unione, nonché con risorse ordinarie da Bilancio statale.

By submitting this proposal, I declare that no significant part or parts of it are recipient of any other public or private funding and that consequently there isn't any so-called double financing pursuant to art. 9 of Regulation (EU) 2021/241, i.e. that there is no duplication in the financing of the same costs by other Euopean Union programs or any other ordinary resources from the State budget.

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Project Type: Starting grant

Project validation result

Message: Success