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Acronym: Combination-Lock01

Full title: Impact of aminoglycosides-based antibiotics combination and protective isolation on outcomes in critically-ill neutropenic patients with sepsis: A randomized 2 by 2 factorial design randomized pragmatic trial.

CLINICAL TRIAL ON CLINICAL TRIAL A MEDICINAL PRODUCT FOR HUMAN USE

Version N°4 du 23/01/2024
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Coordinating Investigator: Michael Darmon

Intensive care and medicine department
Hospital Saint-Louis, APHP
Tel : 01 42 49 94 22
michael.darmon@aphp.fr

Sponsor : AP-HP
and by delegation: Clinical Research and Innovation Delegation (DRCI)
Hôpital Saint-Louis
1, avenue Claude Vellefaux
Référent projet DRCI-Siege: SEYMOUR-INAMO Karine
Tél : 01.44.84.17.42
Courriel : karine.seymour@aphp.fr

Entity responsible for monitoring the trial: Unité de Recherche Clinique (URC)
Hôpital Saint-Louis
Référent projet DRCI-URC : Nabil RAKED
Tél 01 42 49 97 49
Courriel : nabil.raked@univ-paris-diderot.fr

Clinical Research and Innovation Delegation (DRCI)
Hôpital Saint Louis 75010 PARIS

Pharmaceutical coordination	Agence Générale des Equipements et Produits de Santé (AGEPS) Département Essais Cliniques 7, Rue du Fer à moulin 75005 PARIS Secrétariat essais cliniques AGEPS secretariat.dec.eps@aphp.fr Tel: +33 1 46 69 14 02
Entity responsible for Safety	Safety department - DRCI Hôpital Fernand Widal 200, rue du Faubourg Saint-Denis 75475 Paris Sarra DALIBEY, head of safety department Tel : +33 (0)1 40 27 57 85 / Email : sarra.dalibey@aphp.fr

CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE

CLINICAL TRIAL

INTERVENTIONAL RESEARCH PROTOCOL

PROTOCOL SIGNATURE PAGE

Research code number: APHP180690

Title: Combination-Lock01
Impact of aminoglycosides-based antibiotics combination and protective isolation on outcomes in critically-ill neutropenic patients with sepsis: a randomized 2 by 2 factorial design randomized pragmatic trial.

Version N°4 du 23/01/2024

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

Professeur Michael DARMON
MEDECINE INTENSIVE ET REANIMATION
HOPITAL SAINT LOUIS
1 avenue Claude Vellefaux
75475 Paris Cedex 10
Tel. : 01 42 49 94 19/21
Fax : 01 42 49 94 26
RPPS : 10001595247

Coordinating Investigator
Pr Michael Darmon
Médecine intensive et Réanimation
Hôpital Saint-Louis
Paris

Date: 03 / 04 / 24
Signature:

Sponsor
Assistance Publique-Hôpitaux de Paris
Clinical Research and Innovation Delegation (DRCI)
Hôpital Saint Louis
1 avenue Claude Vellefaux
75010 PARIS

Date: 04 / 04 / 2024
Signature:

Yannick VACHER
Responsable adjoint - Pôle Promotion
DRCI

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1 SUMMARY

Full title	Combination-Lock01 - Impact of aminoglycosides-based antibiotics combination and protective isolation on outcomes in critically-ill neutropenic patients with sepsis: A randomized 2 by 2 factorial design randomized pragmatic trial.
Acronym	Combination-Lock01
Coordinating Investigator	*Michael Darmon* *Service de Médecine Intensive et Réanimation* *CHU Saint-Louis, APHP* *Tel : 01 42 49 94 22* *michael.darmon@aphp.fr*
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Sepsis remains the leading cause of ICU admission in neutropenic patients. This condition remains associated with a high morbidity and mortality, with hospital mortality of 60% when vasopressors are required. Full protective isolation (including geographic isolation, technical isolation, high-efficiency air filtration, and digestive decontamination) proved to be efficient in patients with profound and prolonged neutropenia with regard to infection rate. However, these studies are biased and were performed up to 40 years ago. More recent studies, performed in patients with less profound neutropenia, or performed without digestive decontamination or with partial protective isolation led however to negative results. More importantly, isolation has been demonstrated to limit access to patients' room and to be associated with suboptimal monitoring, with increased rate of severe and avoidable adverse events. This may explain the uneven use of protective isolation in hematology ward and expert's suggestion to appraise protective isolation benefits using large well conducted RCT. In neutropenic patients with suspected sepsis, urgent broad antibiotic therapy is mandatory and failure to initiate adequate antibiotic therapy within 1 hour has been associated with a 10 fold increase in adjusted mortality. Current IDSA guidelines recommend using preferentially large anti-pseudomonas beta-lactam therapy. Routine antibiotic combination using aminoglycosides is controversial and not recommended. On one hand, meta-analyses suggested not-only a lack of benefit from this association but also increased rate of renal failure and a trend towards a higher mortality rate with aminoglycosides use. On the other hand, subgroup analysis and low-level evidences studies suggest however a benefit from aminoglycosides in critically-ill patients, patients with severe sepsis, or those with documented gram negative infection. Along this line, both the recent Cochran systematic review and the recent French guidelines focusing on neutropenia management in critically-ill

	patients advocated additional trials in this field focusing in the sickest patients. The current study aims to assess benefits of protective isolation and systematic use of aminoglycosides combination antibiotic therapy in critically-ill patients with cancer-related neutropenia and sepsis or septic shock. To do so, we intend to perform a 2x2 factorial design randomized pragmatic trial comparing on one hand benefits of protective isolation (versus no protective isolation) and in the other hand benefits of systematic aminoglycosides antibiotics combination (versus no systematic combination).
Main objective and primary endpoint	To evaluate the impact on day-90 mortality of two strategies, separately, using a 2x2 factorial design RCT: • Intervention 1 - routine association of aminoglycoside to initial antibiotic therapy when compared to standard of care • Intervention 2 - lack of routine use of protective isolation when compared to standard of care **Primary endpoint**: Day-90 mortality
Secondary objectives and endpoints	To evaluate the impact of the studied interventions, on - Day-28 and hospital outcome - Incidence, severity and duration of AKI - Incidence of clinically apparent loss of hearing - Rate of adherence of hand hygiene - Rate of selected adverse events - Rate of nosocomial bacterial, viral and fungal infection episodes - Organ support during ICU stay and organ support duration - Failure of initial antibiotic therapy - Antibiotic duration - Rate of aminoglycosides overdosage and overuse **Secondary endpoints** - Day-28 and hospital mortality - Incidence and severity of AKI according to KDIGO definition - Major Adverse Kidney Events at day-28 and day 90 (composite of death, new renal replacement therapy, or persistent renal dysfunction). - Incidence of clinically apparent loss of hearing at end of ICU stay and day 90 - Rate of adherence to adequate hand hygiene as assessed by external observer. - Incidence density of selected serious adverse events including unexpected cardiac arrest. - Incidence density of new bacterial, viral or fungal episode. - Number of days free from organ support therapy (mechanical ventilation, vasopressors or RRT) at day 28 - Rate of clinical cure - Frequency of initial antibiotic therapy inadequate as regard to microbiological documentation.

	- Number of day free of antibiotic therapy at day-28 - Duration of aminoglycoside therapy, rate of aminoglycoside overdosage according to residual concentration and overuse when compared to experts recommendations
Design of the trial	Prospective, randomized, open label, controlled, multicenter 2x2 factorial, pragmatic, clinical trial
Population of trial subjects	Adult patients admitted to intensive care
Inclusion criteria	- Age ≥ 18 years - Admitted in one of the participating ICU - Sepsis or septic shock as defined by SEPSIS3 definition - Underlying tumor, allogeneic stem cell transplantation or hematological malignancy - Neutropenia (defined by either absolute neutrophil count <500/mm3 or leucocytes <1000/mm3) related to an underlying malignancy or its treatment - Informed or deferred consent
Exclusion criteria	- Pregnancy and breastfeeding - Moribund patients (death expected within 48 hours by attending physician) - Previous participation to this study - No affiliation to social security - Patients under legal protection according to French Law - Patient having received more than 1 injection of aminoglycosides in the 3 days preceding ICU admission - Contraindication to aminoglycosides as mentioned in SpC section 4.3: o Hypersensitivity to amikacin, to other antibiotics from the aminoglycoside family, or to any excipient from the amikacin used. o Patients with documented allergy to aminoglycosides o Myasthenia gravis o Concomitant administration of intravenous Polymyxin - Delay between onset of sepsis and inclusion>24 hours
Investigational strategy and medicinal product(s)	• Intervention 1 - Association of aminoglycoside to initial antibiotic therapy • Intervention 2 - Lack of routine use of protective isolation (Weak protective isolation)
Comparator strategy and treatment	• Intervention 1 - Antibiotic therapy without systematic adjunction of aminoglycosides • Intervention 2 - Standard of care protective isolation
Expected benefits	Optimize management of critically ill neutropenic patients Broadening of the spectrum of antibiotherapy with aminoglycoside. Absence of protective isolation for monitoring reducing the rate of avoidable events.
Risks added by the trial	Aminoglycosides-based antibiotics combination increases Risk of Acute Renal Failure Absence of protective isolation increasing the theoretical risk of acquired bacterial or fungal infection. Risque D
Scope of the trial	After checking the eligibility criteria, the patients will be randomized according to a balanced scheme and will be allocated in one arm of each intervention:

	- Aminoglycoside: either systematic addition of aminoglycosides to probabilistic antibiotic therapy for a maximum of 3 days, or aminoglycoside only in specific pre-defined indications - Isolation: either protective isolation (geographical, technical, with air filtration) or universal measures expanded, with mask during viral epidemic episodes.
Number of subjects included	340
Number of sites	14 ICUs in France
Duration of the trial	- Duration of participation for each subject (Treatment and Follow-up period)t) :90 days - Total study duration: 33 Months (30 months duration of recruitment + 3 months of follow-up)
Number of enrolments expected per site and per month	0,8
Statistical analysis	According to previous studies by our study group, day-90 mortality in the studied population is expected to be of 60%. Assuming a 15% target effect for each of the interventions compared with their respective control, a type I error rate of 0.05 and a power of 80%, each group should include 170 patients on the basis of a two-sided log-rank test. No correlation is expected between interventions. Only main effects will be estimated, and interaction between interventions tested. Aucune analyse intermédiaire n'est prévue
Sources of funding for the trial	PHRC-K18-102
Trial will have a Data Monitoring Committee	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE TRIAL

Sepsis remains the leading cause of ICU admission in neutropenic patients. This condition remains associated with a high morbidity and mortality, with hospital mortality of 60% when vasopressors are required.
Full protective isolation (including geographic isolation, technical isolation, high-efficiency air filtration, and digestive decontamination) proved to be efficient in patients with profound and prolonged neutropenia with regard to infection rate. However, these studies are biased and were performed up to 40 years ago [1]. More recent studies, performed in patients with less profound neutropenia, or performed without digestive decontamination or with partial protective isolation led however to discrepant results [2, 3]. More importantly, isolation has been demonstrated to limit access to patients' room and to be associated with suboptimal monitoring, with increased rate of severe and avoidable adverse events [2, 3]. This may explain the uneven use of protective isolation in hematology ward and expert's suggestion to appraise protective isolation benefits using large well conducted RCT [2, 3].
In neutropenic patients with suspected sepsis, urgent broad antibiotic therapy is mandatory and failure to initiate adequate antibiotic therapy within 1 hour has been associated with a 10 fold increase in mortality. Current IDSA guidelines recommend using preferentially large anti-pseudomonas beta-lactam therapy. Routine antibiotic combination using aminoglycoside is controversial and not recommended. On one hand, studies meta-analyses suggested not-only a lack of benefit from this association but also increased rate of renal failure and a trend towards a higher mortality rate with aminoglycosides use [4]. On the other hand, subgroup analysis and low-level evidences studies suggest however a benefit from aminoglycosides in critically-ill patients [5], those with severe sepsis [4, 5], or those with documented gram negative infection [4]. Along this line, both the recent Cochran systematic review and the recent French guidelines focusing on neutropenia management in critically-ill patients advocated additional trials in this field focusing in the sickest patients [3, 4].

The current study aims to assess benefits of protective isolation and systematic use of aminoglycosides combination antibiotic therapy in critically-ill patients with cancer-related neutropenia and sepsis or septic shock. To do so, we intend to perform a 2x2 factorial design randomized pragmatic trial comparing on one hand benefits of protective isolation (versus no protective isolation) and in the other hand benefits of systematic aminoglycosides antibiotics combination (versus no systematic combination).

Primary outcome will be on hard clinical endpoints, namely day-90 mortality. Secondary endpoints will includes severity and organ support, rate of acute kidney injury, adherence to hand hygiene, density of serious adverse events, rate of antibiotics adequate as regard to microbiological documentation, rate of hospital acquired infection and new fungal episodes.
According to previous studies by our study group, day-90 mortality in the studied population is expected to be of 60%. Assuming a 15% target effect for each of the interventions compared with their respective control, a type I error rate of 0.05 and a power of 80%, each group should include 170 patients on the basis of a two-sided log-rank test. No correlation is expected between interventions. Only main effects will be estimated, and interaction between interventions tested.

Study feasibility will be ensured by the support of our clinica trial study group (Groupe de Recherche en Réanimation Respiratoire et Onco-hématologique) and by the support of the Saint-Louis University Hospital clinical trial unit. The GRRROH study group is constituted of 34 ICUs, has access to a methodological and biostatistics unit. Several RCTs, included studies funded by PRHC or INCA have been completed and published by this group demonstrating capacity of this group to run and complete large RCTs.

2.1 Hypothesis for the study

We hypothesized that systematic combination with aminoglycosides would allow providing broader spectrum antibiotic therapy, high bactericidal activity and potentially synergistic effect that may translate into higher survival of neutropenic critically-ill patients with sepsis.

We also hypothesized that absence of protective isolation would allow easier access to patients room and opportunity for adequate monitoring, decrease rate of severe adverse events, while proving safe in terms of bacterial and fungal risk that may translate into higher survival of neutropenic critically-ill patients with sepsis.

2.2 Existing knowledge relating to the condition under investigation

Management of Critically-ill Neutropenic Patients

Cancer is a leading cause of death in North America and Europe [6, 7] and cancer patients are at high risk for life-threatening complications, as a result of infection [8], toxicity of intensive treatments [9] or targeted therapies [10], warranting admission to the intensive care unit (ICU). Despite evidences that ICU mortality rates have declined significantly over the last two decades [11, 12], and although number and extent of comorbidities, pre-existing performance status along with organ failure have been demonstrated to be the main prognostic factors in this setting [13–15], neutropenia remains associated with poor outcome [16].
Although meaningful survival has been described in neutropenic patients [17, 18], the prognostic impact of neutropenia remains significant [16]. Neutropenia remains a common side effect of cancer chemotherapy and, although transient, may lead to immune dysfunction. Clinical consequences of neutropenia are well known and include occurrence of sepsis or acute respiratory failure [19], worsening of respiratory status during neutropenia recovery [20], and need for specific management [21]. Neutropenia was found to be an independent risk factor of poor outcome in the general ICU population [22]. In critically-ill cancer patients, despite influence of coexistent mechanisms of immune deficiency, neutropenia was associated with an increase in relative risk of death of 10% [16]. Moreover, neutropenia occurring in critically-ill cancer patients is associated with high mortality after ICU discharge [23].
Prognosis impact of neutropenia along with high post-ICU mortality is partly related to context and underlying malignancy. The recent guidelines focusing on management of neutropenia in critically-ill patients was the opportunity to gather multidisciplinary team including intensive care, hygiene, infectious disease specialist along with hematologist [3]. Despite the vast amount of literature performed in the field of both prevention and management of infectious complications, several areas of uncertainty were noted and several clinical trial area suggested [3]. Among those, potential benefit of protective isolation and systematic aminoglycosides combination in patients with sepsis/septic shock were highlighted by these experts and others authors [2–4].

Current knowledge of systematic aminoglycoside combination antibiotic therapy

Patients with hematological malignancy are at high risk of bacterial infection, sepsis and septic shock [5, 24]. Infection remaining the commonest factor leading to ICU admission. Hence, sepsis and septic shock may be found in 60 to 80% of critically-ill cancer patients with neutropenia [5, 24–26]. In these patients, bacterial infection remains the rule, AKI and antibiotic therapy should be considered as an emergency. Hence, in neutropenic patients with sepsis/septic shock, a single hour of delay to initiate antibiotic therapy is associated with a 10 fold increase in hospital mortality [27].
Several differences deserve to be noted in the ICU setting. Conversely to the general population of neutropenic patients, fever of unknown origin is uncommon in ICU setting, less than 15% of patients being free of clinical or microbiological documentation, and half of them having a microbiologically documented infection [5, 25, 26]. In patients with microbiological documentation. Conversely to the general neutropenic population, a high proportion of

microbiologically documented infection remain related to gram negative bacteria in critically-ill patients [5, 25, 26]. Neutropenic critically ill patients with suspicion of fever or sepsis should therefore be considered at high risk of severe infection and receive an empirical antibiotic therapy including an antipseudomonal -lactam agent with activity against gram-positive bacteria [28].

Sepsis (formerly known as severe sepsis) and septic shock are major causes of morbidity and mortality in intensive care units (ICUs). Early and appropriate infection control is a priority in the management of sepsis and requires adequate early administration of effective antibiotics with a dosing strategy able to achieve therapeutic concentrations at the site of infection [27, 29]. Aminoglycosides are often given as part of empiric therapy for severe sepsis and septic shock, especially if Pseudomonas aeruginosa infection is suspected [30]. Their use is further supported by the emergence of multidrug-resistant bacteria especially in immunocompromised patients [31, 32]. Systematic use of combination therapy with aminoglycoside might increase antibacterial spectrum and bactericidal activity but benefits remain unproven. Moreover, aminoglycosides are associated with risk of AKI, dependent not only from aminoglycosides management but also from concomitant nephrotoxic agents and patients' severity [33]. Despite theoretical benefits, current guidelines no longer recommend systematic aminoglycoside combination antibiotic therapy in the general population of neutropenic patients [28]. In a recent systematic review focused on the general neutropenic patient population, Paul et al. found no benefit of combination therapy in terms of mortality (n=7,186; OR in favor of monotherapy 0.87; 95%CI 0.75-1.02; I^2=0%) [4]. Moreover, combination therapy was associated with an increased in rate of acute kidney injury (n=6,608; OR in favor of monotherapy 0.45; 95% 0.35-0.57; I^2=0%) [4]. Several limits were however noted. In particular, the authors underlined uncommon use of hard clinical endpoint for most of the studies, limited rate of patients with microbiologically documented infection and low rate of patients with severe sepsis or septic shock (excluded from most of the studies) [4]. These limits along with significant benefits of aminoglycosides in patients with pseudomonas aeruginosa infection or severe sepsis when comparable beta-lactam therapy were used, led the authors to recommend specific studies, performed with hard clinical endpoint as primary outcome, in patients with severe sepsis or septic shock [4].

In this line, two low-level evidence studies specifically demonstrated a potential benefit of aminoglycosides in critically ill patients with neutropenia and severe sepsis and/or septic shock [5, 34]. Although experts therefore recommend using combination therapy in this specific subgroup, they also underline the need for studies producing high-grade evidence in this setting [3, 4].

Current knowledge regarding risk and benefits of protective isolation

Most of the studies assessing the benefits of protective isolation were performed more than four decades ago and are at a high risk of bias. Isolation intended to allow care of a patient without germ in a germ-free environment [35]. In particular, these studies aimed to limit risks of bacterial or fungal infections [36–38]. In some of these studies, full protective isolation (including geographic isolation, technical isolation, high-efficiency air filtration, and digestive decontamination) proved to be efficient in patients with profound and prolonged neutropenia with regard to the rate of infection [36, 37], severe infection [36, 37, 39, 40], induction failure, or mortality rate [36, 41]. The benefit of protective isolation was correlated with neutropenia severity, although the impact of functional neutropenia has never been assessed [36]. Several studies led however to discordant results and most of the studies performed with partial protective isolation, especially without digestive decontamination, or outside setting of prolonged and profound neutropenia, however, failed to demonstrate any benefit [40, 42, 43]. Benefits of high-efficiency air filtration have been underlined in several studies performed before the validation of antifungal prophylaxis protocols [38, 44, 45].

A recent meta-analysis performed to assess benefits of protective isolation failed to demonstrate statistically significant benefit of protective isolation in preventing mortality (OR 0.86; 95%CI 0.65–1.14 – results obtained from randomized trial) or risk of fungal infections

(OR 0.57; 95%CI 0.13–2.53 – results obtained from randomized trial) [1]. The authors however underlined the paucity of available data, the limited level of evidences and the need for additional studies in this field [1]. Uncertainty as regard to potential benefits of protective isolation may explain heterogeneity of practices across centres [2]. Hence, in a recent survey, only half of the hospitals housing neutropenic patients had dedicated procedures, two third of hematological ward having dedicated room with air treatment and two-third of these room having appropriate fixed air filtration [2].
Beyond doubt regarding potential benefits of protective isolation, several report, performed with various type of isolation underline that isolation may decrease access to the patients, decreasing both rate of nurse and physician visits, and ultimately increasing rate of severe and avoidable adverse events [46, 47]. Hence, lower level of isolation such contact isolation for multidrug-resistant organisms were found to decrease rate of vital sign recording, rate of physician note, ultimately increasing rate of averse (OR 2.20; 95%CI 1.47-3.30) and preventable adverse events (OR 6.97; 95%CI 3.38-14.70) and decreasing patients' satisfaction (rate of formal complaint: OR 23.5; 95%CI 8.20-66.4) [47]. Similar results were observed in ICU setting, isolation being associated not only with rate of adverse event but with an increase adjusted rate of ventilator acquired pneumonia (sHR 2.1; 95%CI 1.3-3.3) [48]. Last, protective isolation interfere with patients' wellbeing, patients' perception of protective isolation is grim, protective isolation being associated with a high rate of patients' boredom, distress and anxiety [49].
The recent guidelines regarding management of neutropenic patients in ICU, endorsed by both French Society of intensive care (SRLF, SFAR), and by the French Society of Hematology (SFH), the French Society of hygiene (SFHH) and the French Society of infectious disease (SPILF), acknowledged above mentioned limits of current knowledge, recommending with low level evidence use of protective isolation in patients with profound and prolonged neutropenia [3].
Measures recommended by experts included ideally:
1. High-efficiency air filtration [filtration of 99.7% of particles greater than or equal to 0.3 µm; International Organization for Standardization (ISO) class 5 or better]
2. Geographical isolation
3. Technical isolation, including a face mask and a cap

Other measures (including gloves or digestive decontamination) being found to be of debatable interest.
Although protective isolation was recommended, two limits were underlined by experts. First, the experts acknowledged and warned against risk of delayed ICU admission and limited quality of care. Second, the experts advocated need for dedicated high level evidences studies in this setting [1–3].

Rational for performing this study in ICU setting

This study appraises two highly controversial yet widely used and accepted management strategies in severe critically-ill patients with neutropenia [1–4]. The recommendation to use protective isolation was advocated although experts underline remaining uncertainties regarding this strategy efficacy [1–3]. Similarly, systematic combination antibiotic therapy associating an aminoglycoside is widely accepted in the more severe patients, recommended by experts although once again, experts and authors of the last Cochrane Meta-analysis advocated need for additional high degree of evidence studies [3, 4].
Primary endpoint will be a robust and clinically-relevant endpoint, namely 90-day mortality, as advocated by recent Cochran review [4].
Performing this study in critically-ill patients has several strengths:
First, it assesses its feasibility using clinically-relevant endpoints while ensuring adequate statistical power.
It allows performing this trial in patients with highest degree of equipoise, likely to benefit from potentially deleterious treatment such aminoglycoside or protective isolation [3–5], and in whom risk-benefit ratio remain debated by experts [3, 4].

2.3 Description of the population of trial subjects and justification for the choice of subjects

This study appraises two highly controversial yet widely used and accepted management strategies in severe critically-ill patients with neutropenia [1–4]. The recommendation to use protective isolation was advocated although experts underline remaining uncertainties regarding this strategy efficacy [1–3]. Similarly, systematic combination antibiotic therapy associating an aminoglycoside is widely accepted in the more severe patients, recommended by experts although once again, experts and authors of the last Cochrane Meta-analysis advocated need for additional high degree of evidence studies [3, 4].
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It allows performing this trial in patients with highest degree of equipoise, likely to benefit from potentially deleterious treatment such aminoglycoside or protective isolation [3–5], and in whom risk-benefit ratio remain debated by experts [3, 4].

2.4 Summary of the known and foreseeable benefits and risks for the study participants

Standard practices: No systematic aminoglycosides intervention – standard arm:
Antibiotic therapy and prophylaxis will be in line with more recent IDSA and ESCMID guidelines [3, 28, 50]. No systematic aminoglycoside therapy will be provided except in presence of predefined specific organ infection (such intra-vascular infection for example) or drug-resistant infection requiring aminoglycosides.

Protective isolation intervention – standard arm:
Protective isolation will be provided systematically as currently practiced in participating centres. Modality will be in line with recent SRLF guidelines, we will recommend an isolation ideally including:
1. High-efficiency air filtration [filtration of 99.7% of particles greater than or equal to 0.3 µm; International Organization for Standardization (ISO) class 5 or better]
2. Geographical isolation in an individual room
3. Technical isolation, including a face mask and a cap. This approach of isolation will however be pragmatic on the basis of the “best available” level of isolation in line with recommendation, while not delaying ICU admission and patients’ care [3].

Proposed interventions
Aminoglycosides intervention – intervention arm:
Antibiotic therapy and prophylaxis will be in line with more recent IDSA and ESCMID guidelines [3, 28, 50].
Systematic aminoglycoside therapy will be provided for a recommended duration of three days or until microbiological documentation.
Decision to continue beyond day 3 or microbiological documentation will be possible based on presence of predefined specific organ infection (such intra-vascular infection) or drug-resistant infection requiring aminoglycosides use. Aminoglycosides dose will be standardized and systematic pic and residual concentrations measured.
Lack of protective isolation intervention – intervention arm:
Protective isolation will be avoided until ICU discharge is deemed possible. Specific measures regarding nutrition and water protection will be maintained. A high degree of compliance as regard to antifungal prophylaxis guidelines and local standard hygiene procedures will be advocated [3, 50].

Benefits and risk of proposed interventions.

Based on published guidelines and recent meeting from our study group, we believe equipoise remain as regard to the proposed treatments. Sepsis and septic shock are associated with heavy burden both in terms of mortality but also in terms of morbidity. ICU stay is associated with long term consequences including decreased quality of life, prolonged hospitalization and need for re-education. This study may help optimize management of critically-ill neutropenic patients and may help in delineating risk-benefit ratio.

Aminoglycosides antibiotic therapy may help in providing earlier and adequate antibiotic therapy in patients with severe infection, at a cost of demonstrated risk of renal dysfunction [3, 4]. Low level evidence studies and subgroup analysis of meta-analysis however support this hypothesis [5, 21, 34]. Degree of equipoise as regard to potential risk/benefit ratio of aminoglycosides is further underlined by practice in our study group. Hence, in the TRIALOH cohort, focusing on hematological patients, only 29.5% of critically ill patients with shock received systematic aminoglycoside combination (131 of 444) [51].

Protective isolation although widely accepted is poorly performed and validated. In addition, its use cannot be viewed as harmless since isolation is associated with decrease in patients' care and increased rate of preventable adverse event. [3, 47, 48], at the cost of losing a potentially important but poorly demonstrated benefit in term of bacterial or fungal infection prevention [1, 36, 38].

3 TESTED INTERVENTIONS

3.1 Standard practices:

No systematic aminoglycosides intervention – standard arm:
Antibiotic therapy and prophylaxis will be in line with more recent IDSA and ESCMID guidelines [3, 28, 50].
No systematic aminoglycoside therapy will be provided except in presence of predefined specific organ infection (such intra-vascular infection such endocarditis for example) or drug-resistant infection requiring aminoglycosides.

Protective isolation intervention – standard arm:
Protective isolation will be provided systematically as currently practiced in participating centers. Modality will be in line with recent SRLF guidelines, we will recommend for the patients to receive an isolation the maximal available isolation with the aim to provide:
1. High-efficiency air filtration [filtration of 99.7% of particles greater than or equal to 0.3 µm; International Organization for Standardization (ISO) class 5 or better]
2. Geographical isolation in an individual room
3. Technical isolation, including a face mask and a cap. This approach of isolation will however be pragmatic on the basis of the "best available" level of isolation in line with recommendation, while not delaying ICU admission and patients' care [3].

3.2 Tested interventions

Aminoglycosides intervention – intervention arm:
Antibiotic therapy and prophylaxis will be in line with more recent IDSA and ESCMID guidelines [3, 28, 50].
Systematic aminoglycoside therapy using Amikacin at a dose of 25 to 30 mg/Kg per dose, at a rate of a maximum of 1 infusion per day will be delivered.
Recommended duration will be of three days or until microbiological documentation.
Decision to continue beyond day 3 or microbiological documentation will be possible based on presence of predefined specific organ infection (such intra-vascular infection) or drug-resistant infection requiring aminoglycosides use.
Aminoglycosides dose will be adjusted to systematic pic, and reinfusion will be reassessed every day according to residual concentrations. In this line, delay between infusion will be adjusted according to aminoglycosides residual concentrations.
In patients with acute kidney injury, attending physician may decide to restrain use of aminoglycosides to a single aminoglycosides infusion.

Lack of protective isolation intervention – intervention arm:
Protective isolation will be avoided until ICU discharge is deemed possible.
Specific measures regarding nutrition (including avoidance of food consider at risk of fungal contamination) and water protection will be maintained.
Extended universal hygiene measures will be maintained and use of mask will be advocated during viral epidemic periods.
A high degree of compliance as regard to antifungal prophylaxis guidelines and local standard hygiene procedures will be advocated [3, 50].

In case of subsequent ICU admission within follow-up meeting inclusion and without exclusion criteria treatment would be performed according to randomisation arm

4 OBJECTIVES

4.1 Primary objective

To evaluate the impact on day-90 mortality of two strategies, separately, using a 2x2 factorial design RCT:
Intervention 1- routine association of aminoglycoside to initial antibiotic therapy when compared to standard of care
Intervention 2- lack of routine use of protective isolation when compared to standard of care

4.2 Secondary objectives

To evaluate the impact of the studied interventions, on
- Day-28 and hospital outcome
- Incidence, severity and duration of AKI
- Incidence of clinically apparent loss of hearing
- Rate of adherence of hand hygiene
- Rate of selected adverse events
- Rate of nosocomial bacterial, viral and fungal infection episodes
- Organ support during ICU stay and organ support duration
- Failure of initial antibiotic therapy
- Antibiotic duration
- Rate of aminoglycosides overdosage and overuse

5 DESCRIPTION OF THE TRIAL

5.1 Concise description of the primary and secondary endpoints

5.1.1 Primary endpoint

Day-90 mortality

5.1.2 Secondary endpoints

- Day-28 and hospital mortality
- Incidence and severity of AKI according to KDIGO definition
- Major Adverse Kidney Events at day-28 and day 90 (composite of death, new renal replacement therapy, or persistent renal dysfunction).
- Incidence of clinically apparent loss of hearing at end of ICU stay and day 90
- Rate of adherence to adequate hand hygiene as assessed by external observer.
- Incidence density of selected serious adverse events including unexpected cardiac arrest.
- Incidence density of new bacterial, viral or fungal episode.
    - Number of days free from organ support therapy (mechanical ventilation, vasopressors or RRT) at day 28
- Rate of clinical cure
- Frequency of initial antibiotic therapy inadequate as regard to microbiological documentation.
    - Number of day free of antibiotic therapy at day-28
- Duration of aminoglycoside therapy, rate of aminoglycoside overdosage according to residual concentration and overuse when compared to experts recommendations

5.2 Clinical trial methodology

5.2.1 Design of the trial

- *Phase III study*
- Prospective, randomized, open label, controlled, multicentre 2x2 factorial, pragmatic, clinical trial.

- ***Definitions***

Sepsis will be defined according SEPSIS3 definition and as life-threatening organ dysfunction caused by a dysregulated host response to infection [52].
Organ dysfunction will be, in accordance with SEPSIS3 definition, be defined as acute change in total SOFA score ≥2 points consequent to the infection [52].
Septic shock will be defined according SEPSIS3 definition and as sepsis with 1) persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg; and 2) having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation [52].
Neutropenia will be defined as defined by either absolute neutrophil count <500/mm^3, in the absence of formula by leucocytes <1000/mm^3, or expected neutropenia within 48 hours as consequences of cancer chemotherapy [28]
Prolonged neutropenia will be defined as expected neutropenia duration of 7 days or more or by neutropenia in a context of allogeneic stem cell transplantation [3].
Acute Kidney Injury will be defined according to KDIGO guidelines [53].
Clinical cure will be defined as Resolution of clinical signs and symptoms of infection observed at baseline, improvement or lack of progression of clinical infection, and no requirement for additional antibacterial treatment.

Avoiding and reducing biases

Participant identification
The participants in this clinical trial will be identified as follows:
Site number (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

Randomization and stratification
Randomization 1:1:1:1 will be performed centrally via a Web-based randomization system with the use of a pre-specified randomization lists based on permutation blocks, stratified according to expected neutropenia duration, and centre.

Stratification according to neutropenia duration (<7 days, ≥ 7 days – see definition) will allow stratifying according to neutropenia severity expected to participate to both risk of severe infection and to potential benefits of protective isolation. This will ensure comparability of groups as regard to this variable.

Stratification according to centre will allow stratifying according to cluster of practices as regard to both interventions. Thus, measures used for protective isolation is homogeneous across participating ICUs. This will ensure comparability of groups as regard to local practices.

To avoid observer bias, this study being open label, the primary objective will be a hard clinical endpoint. For secondary endpoints at risk to be influenced by observer bias will be assessed by an adjudication committee

To ensure the absence of attrition bias, the primary analysis will be made according to the intention-to-treat principle.

To ensure non-informative right censoring, a reference date for the analysis that achieved so-called administrative censoring will be used for the analysis of time-to-failure data.

To avoid inflating the type I error rate, baseline characteristics (at randomisation) of the two groups will be compared roughly, without formal statistical testing.

Last, in way to ensure feasibility this study is defined as pragmatic trial. Studied population is not focused on severe and prolonged neutropenia, protective isolation being widely used in neutropenic critically ill patients, and although ideal protective isolation according to guidelines is recommended, large variations are expected across centres according to local practices and availability of adequate air filtration. Heterogeneity across practices, in neutropenia severity and cluster according to centres practices will be partly controlled for by stratification

Pragmatic-Explanatory Continuum Indicator Summary (PRECIS2) tool	
Dimension	Assessment of pragmatism
Eligibility	Participant to the trial are largely unselected in way to represent population considered for intervention in daily practice
Recruitment	Centers are committed to adhere to randomization arm despite local practices and beliefs
Setting	Is the usual setting used to manage patients with sepsis or septic shock in our health care system
Organization	Resources, provider expertise and organization of care delivery is in line with those available in usual care
Flexibility in delivery	Flexibility in delivery is anticipated and accepted as part of the protocol
Flexibility in adherence	Adherence of randomization arm will be recorded. Flexibility taking into account local organization is anticipated.
Follow-up	Follow-up is consistent with usual follow-up in the studied population
Primary outcome	Day-90 mortality is consistent with outcome relevant to the participant
Primary analysis	Will be performed as intent-to-treat analysis.

5.2.2 Number of participating sites

Multicentre national study
14 ICUs will participate to this study and recruit patients (see point 4).
An independent adjudication committee will secondarily judge infection control, adequation of antibiotic therapy, rate of acquired bacterial and fungal infection and dose/dosage of antibiotics.

5.2.3 Identification of the subjects

The subjects participating in this study will be identified as follows:
Site number (3 digits) - Sequential selection number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the trial.

5.2.4 Randomisation

All inclusion and non-inclusion criteria will be checked before randomization

When selected, the patient eligibility will be evaluated from inclusion and non-inclusion criteria. Once the consent will be signed by investigator and the participant, or an appointed representative or if inclusion according to deferred consent, the patient will be included and randomised by connecting the eCRF. The patient identification number will be allocated.
Randomization 1:1:1:1 will be performed centrally and carried out using a computerized system in the eCRF website with the use of pre-specified randomization lists based on permutation blocks (the size of which will not be communicated to any physician involved in the patient accrual), stratified on the expected neutropenia duration (<7, ≥ 7 days), and centre. The randomization scheme will be generated by a computer system performed on R (http://www.R-project.org/) set up by the statistical unit at Saint-Louis hospital (Paris, France).

6 PROCEDURE FOR THE TRIAL

Visits will be performed by a study investigator.

6.1 Inclusion/randomisation visit [D1]

The Inclusion/randomisation visit takes place within a maximum of 24 hours following onset of sepsis of any critically-ill cancer patients
During this visit, the investigator will verify the patient's history (medical, surgical and therapeutic) and laboratory test usually carried out for patients care are sufficient to assess eligibility criteria of the patients and report variables required for patients' randomisation.
Randomisation will be stratified according to centre and severity of underlying neutropenia (namely neutropenia duration – see definition chapter).

Whose consent must be obtained	**Who informs the individual and collects their consent**	**When is the individual informed**	**When is the individual's consent collected**
the subject participating in the trial; *or an appointed representative* or Inclusion according to deferred consent	*the principal investigator (Intensivist)* *or collaborating physician declared and trained in the study ICU*	*During Inclusion/randomisation visit* *Or* *As soon as available and able to approve (deferred consent)*	*After time reflexion at least of 15 minutes During Inclusion visit* *Or* *As soon as available and able to approve (deferred consent)*

Baseline assessment will report:
- Patients medical history, comorbidities, reason for ICU admission, suspected site of infection, previously received antibiotics, pre-existing protective isolation, pre-existing or antifungal treatment or prophylaxis, organ failure and organ support at ICU admission, treatment started since onset of severe sepsis.
- Laboratory test including :
    - *Biochemistry : Sodium, Creatinine, Lactates levels (D1 and D3), Bilirubin; CRP; PCT*
    - *Hematology: White cells, Hemoglobin, Neutrophil count, Platelet; Prothrombin time, Hematocrit*
    - *Bacteriology; Culture and antibiogram*

- *Parasitology: Beta-D-Glucan, Galactomanan assay, Culture and antibiogram*
- *Virology: Results of viral infection clinical trial*

- Severity according to SOFA score (and including SOFA score per organ) will be recorded. Markers of bacterial infection (Procalcitonine), and fungal infection (B-D-Glucane and blood Galactomanan) will be monitored.

6.2 Follow-up visits

A follow-up visit will take place until ICU discharge at Day 2, 3, 7, 14 and 28. Those visits will report:
- Patient condition, severity score according to SOFA score, organ support strategies, antibacterial and antifungal agent received by the patients will be recorded.
- Variables related to tested strategies will be noted, including type and modality of geographic and technic isolation, available air treatment, use of aminoglycosides, dosage and residuals of antibiotic dosage, documented bacterial infection and antibiotic susceptibility of microorganism, occurrence of new possible, probable or definite fungal infection as well as side effects of aminoglycosides will be recorded.
Markers of bacterial infection (Procalcitonine) and fungal infection (B-D-Glucane and blood Galactomanan) will be monitored.
- Laboratory test from at Day 2, 3, 7, 14 and day 28 including:
    - *Biochemistry : Sodium, Creatinine, Lactates levels (D3), Bilirubin; CRP; PCT*
    - *Hematology: White cells, Hemoglobin, Neutrophil count, Platelet; Prothrombin time, Hematocrit*
    - *Virology: Results of viral infection clinical trial*

At day 3 (+/- 1 day) during ICU stay, adherence to hygiene procedure will be assessed using: a) monitoring at random time during day of the visit. This monitoring will be based in predefined endpoint, during 30 minutes and performed by a clinical trial assistant; b) consumption of hydroalcoholic gel, gown, gloves, mask and caps.
For patients discharged from ICU before end of follow-up, a minimal set of follow-up will be ensured by ICU physician and clinical trial assistant including:
- Antifungal and antibacterial agents received by patients between ICU discharge and end of follow-up
- Marker of bacterial and fungal infection
- Possible, probable and definite episodes of fungal infection
- Any episode of bacterial infection documented clinically or microbiologically
- Vital status

6.3 End of ICU stay

A visit will take place at the end of ICU stay. This visit will record patient condition at discharge, days of fever, and days with antibiotic therapy, organ support and their duration, ICU-acquired infection, clinical course of infection. Clinically apparent loss of hearing will be searched for.

6.4 End of study visit

This visit will record patient condition at day-90, at hospital discharge along with received days with antibiotic therapy, number of days with fever during hospital stay or until day-90, episodes of bacterial infection as well as occurrence of new possible, probable or definite fungal infection or side effects of aminoglycosides will be recorded. Markers of bacterial infection (Procalcitonine), and fungal infection (B-D-Glucane and blood Galactomanan) will be monitored until end of follow up for any infectious episode until end of follow-up.
During the entire study period, search for viral pulmonary infection will be performed according to clinical picture and epidemic context.

Arm of randomisation will be maintained during ICU stay and for every subsequent ICU admission during entire study period.

An adjudication committee, blinded to randomisation arm, will evaluate adequation of antibiotic therapy to documented infection, compliance antibiotics to guidelines, response to treatment, along with rate and degree of suspicion of acquired episodes of bacterial and fungal infection. Secondarily, the adjudication committee will assess dosage and residuals of aminoglycosides.

For patients discharged from ICU before day 90, status at day 90 will be assessed according to hospital status. If patients are discharged from hospital before day 90, status at day 90 will be first assessed using vital status at next patients' consultation. In case the patients is lost to follow-up between hospital discharge and day 90, news from patients' condition will be obtained by contacting attending physician, and if no news is obtained, by a phone call to patient or patients' next of kin. During day 90 visit, clinically apparent loss of hearing will be searched for. In case of clinically apparent loss of hearing, an otolaryngologist consultation will be performed according to usual clinical practice.

6.5 Expected length of participation, chronology and duration of the study.

Maximum period between screening and enrolment	24 hours
Length of Inclusion period	30 months
Duration of participation for each subject, of which:	90 Days
• Treatment period:	ICU stay
• Follow-up period:	90 Days
Total study duration:	33 Months

6.6 Table or diagram summarising the chronology of the study

Actions	*~~D0~~ D1* ***Baseline visit***	*D2-D3* *1 visit per day*	*D7-D14-D28*	*ICU discharge*	*End of study* *D90*
Information:	*X*				
Signature of the consent form	*X*				
Past medical history	*X*				
*Clinical exam**	*X*	*X*	*X*	*X*	*X*
*Additional examinations**	*X*	*X*	*X*		
Medical procedures (ECG, etc.)*					
Tests(Biochemistry : Sodium, Creatinine, Lactates levels (D1 and D3), Bilirubin; CRP; PCT Hematology: White cells, Hemoglobin, Neutrophil count, Platelet; Prothrombin time , Hematocrit Bacteriology; Culture and antibiogram Parasitology: Beta-D-Glucan, Galactomanan assay, Culture and antibiogram Virology: Results of viral infection clinical trial.)*	*X*	*X*	*X*		
strategy of intervention by aminoglycoside / protective isolation[1]	*X*	*X*	*X*	*X*	*X*
Compliance	*X*	*X*	*X*	*X*	*X*
Adverse events		*X*	*X*	*X*	*X*

**Every test and procedure is in accordance with standard practices.*

1: Arm of randomisation will be maintained during ICU stay and for every subsequent ICU admission meeting inclusion criteria during entire study period. Except of Arm with systematic aminoglycoside therapy will be provided for a recommended duration of three days or until microbiological documentation.

6.7 Distinction between standard care and clinical trial

Every of the intervention and follow up tests /visits are in accordance with current practices. Only lack of isolation and aminoglycoside antibiotic combination is outside the scope of standard practices, and only as regard to the systematic standardization induced by clinical trial.

Procedures and treatments to be provided during the study	**Procedures and treatments associated with <u>standard care</u>**	**Procedures and treatments added for the <u>study</u>**
Treatments	No systematic aminoglycoside therapy and protective isolation	Systematic aminoglycoside (Amikacine) combination and lack of protective isolation*
Consultations	*Every consultations*	
Blood samples	*Every consultations:Biochemistry : Sodium, Creatinine, Lactates levels (D1 and D3), Bilirubin; CRP; PCT* *Hematology: White cells, Hemoglobin, Neutrophil count, Platelet; Prothrombin time,* *Bacteriology; Culture and antibiogram* *Parasitology: Beta-D-Glucan, Galactomanan assay, Culture and antibiogram* *Virology: Results of viral infection clinical trial*	*For arm with Systematic aminoglycoside:* *Aminoglycosides peak and through concentration from D1 to D3* *(maximum 6 samples of 5mL=30mL)*
Imaging, etc.	*None*	*None*
….		

* Both tested intervention are used indifferently in participating ICUs and the tested study drug is used regularly in this setting, sepsis being acknowledge as one of the classical for this drug in this indication in the drug approval (Autorisation de mise sur le marché). Only the systematic use in random fashion is outside standard practices.

6.8 Termination and exit rules

6.8.1 Criteria and procedures for prematurely terminating the study treatment

6.8.2 Different situations

- This study being a pragmatic trial, suspension of tested intervention are allowed assuming: The investigator must document the reason for suspending and resuming the treatment in the subject's source file and the case report form (CRF)
- The subject remains enrolled in the study until the end of the subject's participation: the investigator must document the reason

The investigator must:

- Document the reason(s)
- Collect all endpoints at the moment the subject exits from the study, if the subject agrees
- Schedule further follow-up visits, especially in case of a serious adverse event.

6.8.3 Criteria and procedure for premature withdrawals and exits from the study

- Subjects may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject's best interests.
- This study being pragmatic and analysis will be performed according to intention to treat, failure to comply to proposed intervention will be monitored but will not lead to premature withdrawals or exits from the study.

➔Subject lost to follow-up: the subject cannot be located. The investigator must make every effort to reconnect with the subject (and record his attempts in the source file), at least to determine whether the subject is alive or dead

If a subject exits the trial prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

The case report form must list the various reasons why the subject exited or was withdrawn from the study:

- ☐ Subject's personal reasons
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

6.8.4 Monitoring subjects after the premature termination of treatment

If a subject exits the trial this will in no way affect the standard care received for his/her condition.
In case of severe adverse events, the investigator must notify the sponsor and monitor the subject for 15 days following the premature termination of treatment (to be adapted depending on the study). If treatment is stopped prematurely due to a serious adverse event, a serious adverse event report will be sent to the Vigilance department by e-mail (eig-vigilance.drc@aphp.fr). The serious adverse reaction will be monitored until it is resolved.
If a Data Monitoring Committee has been created, the committee can specify and/or validate the monitoring methods.

6.8.5 Procedure for replacing subjects, if applicable

Subjects who exit study will not be replaced. As regard to the design, range of follow-up and lack of eviction of the study should study drug be interrupted prematurely, this event is expected to be uncommon.

6.8.6 Full or partial cancellation of the study

AP-HP (the sponsor) or the Competent Authority may prematurely discontinue all or part of the trial, temporarily or permanently, upon the recommendation of the Data Monitoring Committee in the following situations:

- first, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the two treatment arms, requiring a reassessment of the benefit-risk ratio for the trial.
- similarly, AP-HP, as the sponsor, or the Competent Authority may prematurely cancel the trial due to the discovery of unexpected facts or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved**.**
- AP-HP, as the sponsor, reserves the right to permanently suspend enrolment at any time if the enrolment targets have not been met.

Irrespective of the reason for cancellation of the trial, follow-up of patients already enrolled will be maintained and analysis will be performed according to analysis plan.

If the study is cancelled prematurely, AP-HP will inform the Competent Authority and the Institutional Review Board of its decision within 15 days, together with justification for the decision and any recommendations from the Data Monitoring Committee.

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria

- Age ≥ 18 years
- Admitted in one of the participating ICU
- Sepsis or septic shock as defined by SEPSIS3 definition
- Underlying tumor, allogeneic stem cell transplantation or hematological malignancy
- Neutropenia (defined by either absolute neutrophil count <500/mm3 or leucocytes <1000/mm3) related to an underlying malignancy or its treatment
- Informed or deferred consent

7.2 Exclusion criteria

- Pregnancy and breastfeeding
- Moribund patients (death expected within 48 hours by attending physician)
- Previous participation to this study
- No affiliation to social security
- Patients under legal protection according to French Law
- Patient having received more than 1 injection of aminoglycosides in the 3 days preceding ICU admission
- Delay between onset of sepsis and inclusion>24 hours
- Contraindication to aminoglycosides as mentioned in SpC section 4.3:
    - Hypersensitivity to amikacin, to other antibiotics from the aminoglycoside family, or to any excipient from the amikacin used.
    - Allergy to aminoglycosides or one of their excipients Myasthenia gravis
    - Concomitant administration of intravenous Polymyxin

In way to reflect equipoise as stated by the experts and to allow study feasibility in this specific population of patients, relative contra-indications of aminoglycosides (sepsis, dehydration, acute kidney injury …) will not lead to study exclusion. Hence, study population is a population of patients with sepsis, having relative dehydration, acute kidney injury and high rate of comorbidities. Excluding these patients would lead to 1/ inclusion of patients for whom there is no doubt as regard to benefit / risk ratio of aminoglycosides; 2/ do not reflect the usual population for whom systematic aminoglycoside combination is debated; 3/ but also exclusion of a severe group of patients for whom, potential aminoglycosides benefits are expected.

Similarly, a systematic testing for pregnancy will be performed at study inclusion but no follow up or systematic contraception will be required. First, the study population is a group of patients for whom pregnancy is unlikely: underlying cancer, use of cancer chemotherapy, neutropenia, sepsis and organ dysfunction; Second, in the unlikely situation a patient would become pregnant after inclusion, the study period (90 days) and pregnancy test at study inclusion will avoid having any patients beyond first trimester in the study, period at risk when it comes to aminoglycosides; And last, Imposing for this study specific contraception will carry risk of imposing a specific therapy outside standard practices, risk benefit of this later disfavoring contraception.

7.3 Recruitment methods

Source: Patients admitted to the participating ICUs will be included in this study if the meet eligibility criteria.
Anticipated duration of recruitment
30 Months
Planned number of patients/observations to be recruited: 340 Patients
Feasibility According to previous studies by our group, up to 1500 cancer patients were admitted annually in the participating centres including 40% of neutropenic patients of whom 80% had sepsis and neutropenia (500/year). Assuming a conservative hypothesis, a 18 months period may allow inclusion of scheduled number of patients.

	Number of subjects
Total number of subjects to be included	*340*
Number of sites	*14*
Enrolment period (months)	*30*
Number of subjects/site	*25*
Number of subjects/site/month	***0.8***

Expected number of eligible patients in the centres						
	Name	Surname	Town	Country	Expected recruitment/month	Total
	SOUWEINE	Bertrand	Clermont-Ferrand	France	1	18
	MOKART	Djamel	Marseille	France	3	54
	KLOUCHE	Kada	Montpellier	France	1	18
	DECAVELE	Maxens	Paris	France	2	36
	DARMON	Michael	Paris	France	3	54
	PEREZ	Pierre	Nancy	France	1	18
	NSEIR	Saad	Lille	France	1	18
	MURGIER	Martin	Saint-Etienne	France	1	18
	ARGAUD	Laurent	Lyon	France	2	36
	BRUNEEL	Fabrice	Versailles	France	1	18
	NYUNGA	Martine	Roubaix	France	2	36
	KOUATCHET	Achille	Angers	France	2	36
	PENE	Frederic	Paris	France	2	36
	BIGE	Naike	Paris	France	1	18

8 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

8.1 The investigational medicinal product : Amikacin 1 g, powder for solution for infusion

Aminoglycosides will consist of Amikacin.

8.1.1 Presentation

Amikacin is packaged in vials containing 1g of amikacin (powder for solution for infusion).

8.1.2 Posology and administration

Amikacin will be used intravenously, at the daily dose of 25-30 mg/Kg, in a single injection.
Treatment will be recommended to be maintained for a maximum of 3 calendar days but may be stopped earlier in case of bacterial identification.
Pick and Residual concentration will be measured (30 minutes after infusion for the former and every 24 hours after infusion for the later).

Infusion will be performed on the basis of an injection a day, except in case of elevated residual concentration.
Should elevated residual concentration preclude aminoglycosides infusion, the treatment will not be prolonged accordingly.

8.1.3 Supply

Amikacin is provided by the Sponsor.
Amikacin will be specifically labelled for use in the clinical trial and supplied to all investigational sites by the Sponsor (DEC-AGEPS).

8.2 Traceability information for the investigational medicinal product(s)

A log-book recording infusion date and hour as well as lot number of the received drug will be used to ensure information traceability.

Traceability of dispensing will be carried out by theSponsor

8.3 Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including emergency medications

Cf - RCP amikacine

8.4 Methods for monitoring compliance with the treatment

Pick and Residual concentration will be measured (30 minutes after infusion for the former and every 24 hours after infusion for the later).

9 EFFICACY ASSESSMENT

9.1 Description of parameters for assessing efficacy endpoints

Primary endpoint is day-90 mortality.

Secondary endpoints are:
1-objective :
- Day-28 and hospital mortality
- Incidence and severity of AKI according to KDIGO definition
- Major Adverse Kidney Events at day-28 and day 90 (composite of death, new renal replacement therapy, or persistent renal dysfunction).
- Rate of adherence to adequate hand hygiene as assessed by external observer.
- Incidence density of selected serious adverse events including unexpected cardiac arrest.
- Number of days free from organ support therapy (mechanical ventilation, vasopressors or RRT) at day 28
- Number of day free of antibiotic therapy at day-28

2- Subjective and assessed by an adjudication committee blinded to randomization arm:
- Incidence density of new bacterial, viral or fungal episode
- Rate of clinical cure
- Frequency of initial antibiotic therapy inadequate as regard to microbiological documentation.
- Duration of aminoglycoside therapy, rate of aminoglycoside overdosage according to residual concentration and overuse when compared to expert recommendations

Beyond clinical outcomes, biological monitoring allowing efficacy data will include:
- Aminoglycoside dose received by patients and residual concentration from day1 to day 3
- Documented bacteria and antibiograms during the entire study period
- B-D-Glucan, Procalcitonine, Galactomanan measured at Day 1, Day 3, Day 7, Day 14 and Day-28 through ICU stay
- Documented bacterial, viral and fungal infections during the entire study period

10 SPECIFIC COMMITTEES FOR THE TRIAL

10.1 Scientific Committee

Members: Michael Darmon, Elie Azoulay, Djamel Mokart, Jerome Lambert , Fabrice Bruneel, Jean-Ralph Zahar, Achille Kouatchet
Role: determine the objective, write the protocol, recommend changes to the protocol during the trial.
Member of this committee will ensure adequate expertise in field of Intensive Care, management of critically-ill Cancer Patient, Hygiene, Infectiology and Antibiotic management
Operating procedures:

10.2 Steering Committee

Members: M. Darmon, E. Azoulay, S Chevret, J Lambert and a sponsor's appointed representatives for the trial.

Roles
- *Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.*
- *Propose procedures to be followed during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority.*

10.3 Endpoint Adjudication Committee

An adjudication committee will be appointed including a haematologist, a hygiene specialist, and infectious disease specialist and an intensivist will be tasked to define non-objective secondary objectives while being blinded to randomization arm.

11 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

11.1 Definitions

According to Article 2 of the Regulation (EU) N° 536/2014:

- **Adverse event**

Any untoward medical occurrence in a subject, to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

- **Serious adverse event**

Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death

- **Unexpected serious adverse reaction**

A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information
COMPETENT AUTHORITY
According to Article 53 of the Regulation (EU) No 536/2014:

- **Unexpected event**

An unexpected event which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 42. That

notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

According to Article 54 of the Regulation (EU) No 536/2014:

- **Urgent safety measure**

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects. The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken.
That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

11.2 The role of the investigator

The investigator must **assess the seriousness criteria of each adverse event** and record all serious and non-serious adverse events in the case report form.
The investigator must **document** serious adverse events **as thorough as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the severity** of the adverse events by using:
- general terms:
    - *Mild: tolerated by the patient, does not interfere with daily activities*
    - *Moderate: sufficiently uncomfortable to affect daily activities*
    - *Serious: preventing daily activities*

The investigator must assess the **causal relationship** between the serious adverse events and the investigational medicinal product or the study procedure.

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following causality terms

- Certain
- Probable/likely
- Possible
- Unlikely (not ruled out).

These terms are defined as follows (extracted from the WHO-UMC causality categories, version dated 17/04/2012).

Table: WHO-UMC causality categories (extract)

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake ** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
** Or study procedures

11.2.1 Serious adverse events that require a notification without delay by the investigator to the sponsor

the investigator must notify the sponsor **without undue delay but not later than withing 24 hours on the day the investigator becomes aware** of any serious adverse event which occurs during a trial as described in article 41 of regulation (EU) N°536/2014 with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

For this study only serious adverse events occurring during ICU stay will be collected

A serious adverse event is any untoward medical occurrence that:

1- results in death 2- is life-threatening 3- requires inpatient hospitalisation or prolongation of existing hospitalisation 4- results in persistent or significant disability/incapacity 5- is a congenital anomaly/birth defect

Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, require the investigator to notify the sponsor without delay.

11.2.2 Specific features of the protocol

11.2.2.1 Other events that require the investigator to notify the sponsor without delay

- **Adverse events judged as being "medically significant":**

✓ Probable or definite fungal infection according to EORTC criteria
✓ Death considered by the investigator as directly related to a bacterial infection

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, according to the same modalities and within the same timeline as for serious adverse events (see above).

- **In utero** exposure

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any pregnancy that occurs during the trial, even if not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be reported to the sponsor.

11.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are simply recorded in the case report form**.** A CRF extraction of these serious adverse events will be realized every 3 months (see below).

Severe AKI (requiring Renal replacement therapy) and acquired microbiologically documented bacterial infections not directly responsible for death) and not probable or definite fungal infections will be notified to the sponsor through CRF extraction.

- *Normal and natural course of the condition*:

Special rules for trials with a high mortality rate (e.g. morbidity/mortality studies whose primary endpoint is mortality; trials conducted in an emergency setting upon patient enrollment; low risk trials conducted in a patient with a high mortality risk):

The primary objective of the trial is to evaluate the impact on day-90 mortality of two strategies, separately, using a 2x2 factorial design RCT:

- Intervention 1 : routine association of aminoglycoside to initial antibiotic therapy when compared to standard of care
- Intervention 2 : lack of routine use of protective isolation when compared to standard of care

The mortality rate of the condition under investigation (sepsis or septic shock) is 60% at day-90 (see chapter 10.2.).

It is planned to include 340 subjects.

The study procedures are systematic aminoglycoside combination and lack of protective isolation; therefore, **deathsnot directly related to microbiologically documented acquired bacterial infection do not need to be notified to the sponsor without delay but will be recorded in the case report form.**

A CRF extraction of deaths will be realized every 3 months by Clinical Clinical trial Unit (with randomization group, cause of death and investigator's assessment)

These data will be sent to the Data Safety Monitoring Board members and to the sponsor's Safety Department (expertisecsi.drc@aphp.fr).

If there is any imbalance between the randomization groups or the mortality rate is higher than expected affecting the safety of trial subjects and which requires the sponsor to take urgent safety measures, the COMPETENT AUTHORITY will be informed about the emerging safety issue without delay.

- *Special circumstances*

- Hospitalisation for a pre-existing illness or condition
- Hospitalisation for a medical or surgical treatment scheduled prior to the trial
- Admission for social or administrative reasons

- *Adverse events during the trial possibly related to treatments/acts prescribed as a part of the patient's standard care*

The investigator as health care professional must notify these events to the appropriate health surveillance institution according to the situation. Examples: Agence Régionale de Santé, quality department of your hospital, Centre Régional de Pharmacovigilance, local correspondent of the materiovigilance unit (COMPETENT AUTHORITY), etc.

11.2.2.3 Period during which the investigator must send notification of SAEs to the sponsor without delay

The investigator notifies the sponsor without delay of all the serious adverse events listed in the corresponding section:

- starting from the date on which the subject signs the consent form
- until discharge from ICU and within a maximum of day 90
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities)

11.2.2.4 Procedures and deadlines for notifying the sponsor

The investigator should initially complete a SAE reporting form (contained in the case report form). This report must be signed by the investigator.

The investigator must complete every section of the SAE form so that the sponsor can carry out the appropriate assessment.

The initial report sent to the sponsor must be rapidly followed up by one or more additional written reports describing the course of the event and any complementary information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional exams, etc.). These documents must be anonymized. In addition, the investigator must state the study acronym and the number and initials of the study participant on each paper of the attached document..

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has terminated his participation in the trial.

The initial report, the SAE follow-up reports and all other documents must be sent to the sponsor's safety Department by e-mail (eig-vigilance.drc@aphp.fr). It is possible to send the SAE to the AP-HP's Safety department by fax No. +33 (0)1 44 84 17 99 only in case of unsuccessful attempt to send the SAE by e-mail. This is to avoid duplicated reports.

For trials which use e-CRF
- the investigator completes the SAE report form in the e-CRF, then validates, prints and signs the form before sending it by mail;
- In case of failure to connect to the e-CRF, the investigator should complete, sign and send the SAE report form to the safety Department. As soon as the connection is restored, the investigator must complete the SAE report form in the e-CRF.

The investigator must comply with all requests for additional information from the sponsor.
For all questions relating to an adverse event report, the safety Department can be contacted via email at vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the "Follow-up form for reporting a pregnancy occurring in a clinical trial".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy ends, and must notify the sponsor of the outcome of the pregnancy, using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy report form, the SAE follow-up forms and any other documents will be sent to the sponsor using the same modalities as described above.
If it was the father who was exposed, the investigator must obtain the mother's permission before collecting information about the pregnancy.

11.2.3 Role of the sponsor

The sponsor, represented by its safety Department, shall continuously assess the safety of each investigational medicinal product throughout the trial.

11.2.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and investigational medicinal product *and/or study procedures* and any other treatments,
  All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expectedness assessment** of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.
  The sponsor, acting through its safety Department, assesses the expectedness of the serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product(s):

- refer to the SmPC for Amikacin, from the COMPETENT AUTHORITY website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php); otherwise, use the SCP from Vidal
  Main risk of aminoglycosides are risk increasing rate or severity of acute kidney injury, and risk of anaphylactic reaction.

  For this study new episodes of severe AKI will be monitored and will be sent to the DSMB using the e-CRF.

❖ The serious adverse events associated with the study procedures (lack of protective isolation) are:

Risk of favouring emergence of bacterial or fungal infection.

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs) via Eudravigilance, within the regulatory time frame, to the competent authority:

- in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction;
- in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;
- in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening
- in the uncompleted case of fatal or life-threatening suspected unexpected serious adverse reactions, all additional information to complete this case have to be reported as soon as possible and in any event not later than eight days after the initial report

All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 15 days starting from when the sponsor had this information

The sponsor must notify all the investigators about any information that could adversely affect the safety of the trial subjects.

11.2.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

The sponsor will report in CTIS platform without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

11.2.3.3 Annual safety report

The sponsor must prepare once yearly throughout the clinical trial duration an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- an analysis of safety data concerning trial subjects
- a description of the patients included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial,

The sponsor produce one annual safety report (Development Safety Update Report - DSUR) for one clinical trial.

The report must be submitted in CTIS no later than 60 days after the anniversary of the date on which the competent authority authorised the trial.

11.2.4 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) can be set up by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of a DSMB to the Competent Authority and to the Ethics committee.

A DSMB will be set up for this trial. The DSMB must hold its first meeting before the first subject is enrolled. The DSMB's preliminary meeting should take place before the protocol submission to competent health authority and Ethics committee.

Important: The DSMB has a consultative role. The decision concerning the conduct of the clinical trial relies on the sponsor.

A DSMB will be convened for this biomedical clinical trial because this is studie where study risk level is "D". The DSMB will hold its preliminary meeting before the first inclusion of the first patient.

General information about the DSMB: The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the clinical trial, but the sponsor remains the only decision maker. The recommendations that the DSMB can make are:

- to continue the clinical trial with no modifications
- to continue the clinical trial with a modification to the protocol and/or to the monitoring of patients
- to temporarily halt inclusions
- to permanently terminate the clinical trial in light of:
    - safety data: serious adverse reactions
    - efficacy data: proven futility or efficacy

The DSMB is appointed by the sponsor and is made up of at least 3 people with no connection to the clinical trial, including at least one specialized clinician in the pathology being studied and one specialist in the studied medication being studied (or a pharmacologist/pharmacovigilance specialist), and possibly a methodologist/biostatistician, particularly in the case of interim analysis.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the clinical trial. The DSMB must hold its preliminary meeting before the first inclusions of the first patient and ideally before the protocol is submitted to the competent authority and the CPP. The committee's agenda will be as follows:

Definition of the DSMB's missions:

- Validation of the clinical trial methodology:
  The proposed methodology for the clinical trial will be validated by the IOC so that it does not jeopardize the safety of patients, in particular relating to the inclusion and randomization methods.

- Validation of tolerance monitoring methods:
    - nature of the evaluated parameters
    - frequency of the evaluations, consultation schedule
- Validation of termination criteria:
    - criteria for terminating a patient's participation for tolerance reasons
    - criteria for the temporary or permanent termination of the clinical trial (leading to the establishment of certain recommendations ("stopping rules"))
- Modification of the protocol and recommendations:
  In light of the analysis of tolerance data for the clinical trial, the DSMB can, when applicable:
    - Propose substantial modifications in order to modify certain data, in particular relating to the protocol (inclusion and non-inclusion criteria, monitoring, additional exams, etc.). Likewise the DMSB can issue any recommendations it deems useful in order to best ensure the safety of the clinical trial patients and to maintain a favourable benefit-risk balance throughout the clinical trial.

Definition of the DSMB's operating methods:

- meeting types (open session, then closed sessions) and schedule
- desired methods and format of SAE notification from the sponsor to the DSMB

The DSMB appoints its chairman at the first meeting. The sponsor retains decision-making authority. When applicable, the sponsor delivers its decision, with justification, and DSMB reports to the Competent Authority and the CPP.

The DSMB of the study consists of the following way:

Name	Localisation	Spécialité
Dr Benoit Dominique	Intenleve zorg –UZ Gent De Pinte aan 185- 9000 Gent	Réanimateur
Dr BOUADMA Lila	Assistance publique-hôpitaux de paris 46 Rue Henri Huchard (HU PARIS NORD SITE BICHAT APHP) 75018 Paris	Interniste
Dr Tezenas Du Montcel Sophie	Assistance publique-hopitaux de paris HU-Paris Salpetrière site Salpetrière ap-hp 47 boulevard de l'Hôpital 75013 Paris	santé publique et médecine sociale

The first meeting of the DSMB was held **before the inclusion of the first patient in the clinical trial.** The operating procedures of the DSMB have been defined and are described in the Charter for the maintenance of the DSMB of the study.

Records of the meetings of the DSMB will be sent regularly to the COMPETENT AUTHORITY.

12 DATA MANAGEMENT

12.1 Data collection

Data will be collected in an electronic case report form (e-CRF), devised by the study coordinator in collaboration with URC-St Louis.

12.2 Identification of data recorded directly in the CRFs which will be considered as source data

The data recorded directly in the CRF which will be considered as source data are those reporting on section 5.1.to 5.4.

12.3 Right to access source data and documents

12.3.1 Access to data

In accordance with GCP and appendix 1 of the European Regulation N°536-2014:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority.
- the Sponsor declares that investigators and participating institution will ensure the persons in charge of monitoring, quality control and auditing or inspecting the clinical trial have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force

12.3.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

Source documents relevant to the trial will be : medical files, original laboratory test results, medical imaging reports, ICU charts, dedicated forms relating to hygiene measure compliance and adverse event.

12.3.3 Data confidentiality

The persons responsible for the quality control of clinical studies will take all necessary precautions to ensure the confidentiality of information relating to the investigational m
edicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy
During and after the clinical trial , all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered anonymous.
Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant’s initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

12.4 Data processing and storage of documents and data

12.4.1 Identification of the data processing manager and the location(s)

The database will be handled by, and only by, Jerome Lambert, who will be responsible for data storage. The statistical analysis, and the tables and figures for the study report will be handled byJ Lambert . He will be in close contact with the Data Safety and Monitoring Board and with the statistical editors of the journal to which the study report will be submitted for publication

12.4.2 Data entry

Data entry will be carried out on electronic media via a web browser by staff dedicated to this task in each centre with a restricted access to investigators.

12.4.3 Data processing (CNIL, the French Data Protection Authority) in France

This trial is not governed by the CNIL "Reference Method for processing personal data for clinical studies" (MR-001, amended)" and the sponsor must obtain approval from the CNIL, because of emergency situation in accordance with Article L.1122-1-2 can be carried out in the case where the patient could not consent and an appointed representative (family members/trustworthy person) is not be present.

All personal data for this trial will be processed in accordance with Chapter IX of the amended French Data Protection Act of 6 January 1978 (articles 53-61).

12.4.4 Archiving

The specific documents for a clinical trial on a medicinal product for human use will be archived by the investigator and the sponsor for *15 years* after the end of the trial.

This indexed archiving includes, in particular:

- A sealed envelope containing the originals of all information sheets and consent forms signed by all individuals at the site who participated in the study for the investigator;
- One copy of all the information sheets and signed consent forms signed for all individuals at the site who participated in the study for the sponsor;
- "Study" binders for the Investigator and the sponsor, containing:
    - all successive versions of the protocol (identified by version no. and date), and its appendices
    - the COMPETENT AUTHORITY authorisations and CPP decisions
    - correspondence
    - the enrolment list or register
    - the appendices specific to the study
    - the final study report
- The data collection documents

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12.5 Ownership of the data

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

13 STATISTICAL ASPECTS

13.1 Planned statistical methods, including the timetable for any planned interim analyses

13.1.1 Minimizing biases

The most effective design technique for avoiding selection bias and allowing causal inference is randomization. To ensure the absence of attrition bias, the primary analysis will be made according to the intention-to-treat principle.
To ensure non-informative right censoring, we have defined 90-day survival as the main endpoint, so that censoring will be fixed, and no informative censoring could be introduced for the analysis of time-to-failure data
To avoid inflating the type I error rate, baseline characteristics (at randomization) of the two groups will be compared roughly, without formal statistical testing. Given we are only interested in the main effects of each intervention no correction to multiple analyses has to be done.

13.1.2 Type of comparisons

The main comparison based on the intention-to-treat principle will compare the intervention arm to the control arm. To handle the study design, analysis of each intervention will use stratified test statistics [55]. The Gail and Simon test will allow assessing the existence of any interaction between interventions and outcome effects [56].
Secondary and exploratory comparisons of the primary endpoint will look for treatment-by-covariate interactions according to the severity of sepsis (sepsis vs. septic shock), severity of neutropenia (prolonged vs. not).

Finally, an exploratory per-protocol analysis will be performed

13.1.3 Interim analyses

No interim analysis will be performed. The final analysis will be started after inclusion of the planned number of patients.

13.1.4 Control for heterogeneity in isolation and antibiotics practices

This study is designed as a pragmatic study aiming to accept heterogeneity related to real life practices, recording data related to this heterogeneity and if required adjusting secondarily according to these differences. Several measures are therefore planned to decrease influence of heterogeneity across participating centers:

- First, stratification by center will ensure each arm is equally represented for each center partially adjusting for clustering among centers which account in the above mentioned heterogeneity.
- In addition, national and international guidelines will be provided to local investigators ensuring practices across center does not deviate excessively from recognized standard of care.
- Last, implemented isolation strategy, antibiotic therapy, and adequation of this later with clinical and microbiological documentation will be secondarily assessed by an adjudication committee including an independent hematologist; an intensivist specialized in infectious diseases and a hygiene specialist.

13.1.5 General principles

In general, quantitative variables will be described by their median and first and third quartiles and qualitative variables will be described by the frequencies of the modalities and the associated percentages.

The epidemiological and clinical characteristics of the patients included will be described by group, without statistical tests being carried out. Violations of the protocol, causes of abandonment and loss of sight and characteristics of these patients will be detailed.

Tests for treatment-by-effect interactions, using the Gail and Simon test will be performed [56, 57] on each endpoint checking the absence of interaction between both randomizations. In case of qualitative interaction, then separate point and interval estimates in the four subgroups will be reported.

13.1.6 Analysis of primary outcome

Day-90 mortality between groups of one intervention will be compared using a logistic model stratified on the groups of the other intervention. Odd Ratios and 95% CI will be given. Wald tests will be performed.

13.1.7 Analysis of secondary outcomes

- Day-28 and hospital mortality between groups of one intervention will be compared using a multivariable (logistic) regression analysis adjusting on the other randomization arm which is required in order to obtain correct estimates of the effects and their standard errors. Odd Ratios and 95% CI will be given.

- Incidence and severity of AKI according to KDIGO definition will be estimated using cumulative incidence estimator considering death without AKI as a competing risk. Incidences between groups of one intervention will be compared using a multivariable Fine and Gray model adjusted on the other intervention. Sub Hazard Ratios and 95% CI will be given.

- Major Adverse Kidney Events at day-28 and day 90 (composite of death, new renal replacement therapy, or persistent renal dysfunction) between groups of one intervention will be compared using a multivariable logistic model to adjust on the other randomized intervention. Odd Ratios and 95% CI will be given.

- Rate of adherence to adequate hand hygiene as assessed by external observer will be estimated with its exact 95%CI

- Incidence density of selected serious adverse events including unexpected cardiac arrest will be estimated using cumulative incidence estimator considering death LATA as a competing risk. Incidences between groups of one intervention will be compared using a multivariable Fine and Gray model adjusted on the other intervention. Sub Hazard Ratios and 95% CI will be given.

- Incidence density of new bacterial, viral or fungal episode will be estimated using cumulative incidence estimator considering death without new bacterial, viral or fungal episode as a competing risk. Incidences between groups of one intervention will be compared using a multivariable Fine and Gray model adjusted on the other intervention. Sub Hazard Ratios and 95% CI will be given.

- Number of days free from organ support therapy (mechanical ventilation, vasopressors or RRT) at day 28 will be compared between groups of one intervention using the van Elteren test, a stratified Wilcoxon–Mann–Whitney test, can be used to adjust for the stratum effect due to the groups of the other intervention.

- Rate of clinical cures will be estimated then compared using maximum likelihood estimator and Mantel-Haenszel test stratified on the group of the other intervention

- Frequency of initial antibiotic therapy inadequate as regard to microbiological documentation. Frequency of initial antibiotic therapy inadequate will be estimated with its exact 95%CI

- Number of days free of antibiotic therapy at day-28 will be compared between groups of one intervention using a van Elteren test stratified on the group of the other intervention.

- Duration of aminoglycoside therapy, rate of aminoglycoside overdosage according to residual concentration and overuse when compared to experts recommendations will be estimated using cumulative incidence curves in a competing risks setting due to first deaths treated as informative censoring observations.

Finally, an exploratory per-protocol analysis will be performed

13.1.8 Subgroup analyses

Pre-planned subgroup analyses will be performed on the following sub-population.
- According to Neutropenia duration (<7 days or ≥ 7 days)
- According to Sepsis definition (Sepsis or septic shock as defined by SEPSIS3 definition)
- According to the need for invasive mechanical ventilation at day 1. This analyses will be based on a landmark at day 1 (including only patients alive at day 1)
- According to Use of High filtration during protective isolation

Description of patients will be performed according the treatment arm within each subgroups, Treatment effect will be estimated within each subgroup. Interaction of the treatment effects with the subgroup definition will be tested using Gail and Simon qualitative and quantitative tests. In case of significant interaction test, treatment effect will tested within the subgroups.

13.2 Hypotheses for calculating the required number of subjects, and the result

We aim only to estimate the marginal effects of each intervention, and not to make any pairwise comparison or testing the benefit of the combination. Thus, all randomized patients will be included in the estimation of the effect of treatment and, the 2×2 factorial design has essentially the same power as a corresponding simple randomized trial which would only randomize one intervention [55].

Our hypothesis is that both interventions will decrease hospital mortality by 15% in neutropenic critically-ill cancer patients. In previous work, use of aminoglycosides during severe sepsis were associated with a lower adjusted mortality (OR 0.16; 95%CI 0.05-0.50) [5]. In a recent Cochran Meta-analysis, although performed in subgroup receiving comparable beta-lactam therapy, point-estimate in favour of combination therapy was an OR of 1.34 (95%CI 1.03-1.74) for gram negative infection and 1.48 (95%CI 1.12-1.96) in patients with severe neutropenia. Effect of absence of protective isolation on outcome can only be estimated indirectly. It must be noted however that simple contact isolation increase rate of adverse event by 50 to 100% after adjustment for confounders [47, 48] while experiencing adverse event is associated with a threefold increase in adjusted mortality in ICU setting (OR 3.09 ;95%CI 1.30-7.36) [54].

According to previous studies by our group, expected day-90 mortality in absence of intervention is of 60%. Sample size computation was based on the assumption of no interaction between the interventions, based on separate calculation based on a 15% target effect size for each of the interventions compared with their respective controls. Controlling for a type I error rate at 0.05 and a power of 80%, each group should include 170 patients, on the basis of a two-sided log-rank test.

Recruitment will last 30 months, with 3 months of additional follow-up.

13.3 State whether subjects who exit the study prematurely will be replaced and in what proportion.

Analysis will be performed in intent to treat analysis on all the included patients except patients who withdraw consent. Only patients who withdraw their consent during the inclusion phase of the study will be replaced.

13.4 Anticipated level of statistical significance

Type I error rate 0.05, on the basis of bilateral formulation

13.5 Method for taking into account missing, unused or invalid data

Analysis sets
According to the intention-to-treat principle, the full analysis set, that is, the set of patients whose data are included in the main primary analysis is composed of all randomized patients except those who withdraw consent.

The per protocol analysis set is composed of patients who completed the strategies originally allocated.

Missing values and outliers
Missing values for the main outcome measure will be handled using time-to-event methods in which each patient contributes to the estimate of failure time distribution until he/she is lost-to-follow up or withdrawn from the study. Missing values for predictors will be imputed using multiple imputation techniques

13.6 Management of modifications made to the analysis plan for the initial strategy.

Analysis plan will be performed in accordance to pre-written protocol. Analyses performed after initial strategy will be considered and reported as post-hoc analysis

13.7 Selection of populations

According to the intention-to-treat principle, the full analysis set, that is, the set of patients whose data are included in the main primary analysis is composed of all randomized patients except those who withdraw consent.

14 QUALITY CONTROL AND ASSURANCE

Every clinical trial sponsored by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored clinical trial .

14.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the trial. The sponsor must implement a quality assurance system to best monitor theimplementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Clinical trial Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits..
The purpose of monitoring the study, as defined in the Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the clinical trial participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

14.1.1 Strategy for site opening

The strategy for opening the sites is determined using the tailored monitoring plan. It will be performed by the CRA from the URC-DRC from Saint Louis hospital.

14.1.2 Scope of site monitoring

In the case of this risk study **which is considered level D risk,** the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a clinical trial monitoring level to be implemented: level « High »

14.2 Quality control

A Clinical Clinical trial Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical trialAssociate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

14.3 Case Report Form

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

14.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.
These non-compliances will be managed in accordance with the sponsor's procedures.

The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

14.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.
An audit can be carried out at any time by individuals appointed by the sponsor who are not associated with the study managers. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

14.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of

Health Professionals, for France). The CV must include any previous involvement in clinical clinical trial and related training.
Any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented.

Each investigator will agree to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki. Each investigator will give the sponsor's representative a GCP certificate dated fewer than three years ago.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14.7 Suitability of the facilities

Before starting the study, each clinical trial sites will give the sponsor's representative a duly justified written statement on the suitability adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise.

15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Methods for informing and obtaining consent from the clinical trial participants

According to article 29 of European regulation N°536/2014, No clinical trials on medicinal products for human use can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in article 29.2 of the European Regulation.

The person's freely-given, written, and informed consent will be obtained during inclusion/randomisation visit by the investigator, or by a physician representing the investigator, before the person is enrolled on the study.

The person will be granted a reflection *at least 15 minutes and a maximum of 24 hours* period between the time when the subject receives the information and the time when he or she signs the consent form at inclusion visit

In addition, the investigator will specify in the clinical trial participant's medical file the methods used for obtaining their consent [or the consent of any other person *in the cases set forth by article European regulation N°536/2014 (art. 29 and following)* as well as the methods used for providing information with a view to obtaining consent.

A copy of the information note and consent form, signed and dated by the clinical trial participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

Since this trial is performed in an emergency setting and may concern adult incapable of giving consent:

Studies in emergency situations: Article 35 of the European regulation N°536/2014 : If the person is unable to give his or her written consent, consent may be obtained, in descending order of priority, from a legal representative, family members or trustworthy person. These persons must have no connection whatsoever to the investigator or the sponsor

When the patient was enrolled in emergency situation, consent of family members or trustworthy person will be sign before inclusion. If a legal representative is not present, the deferred consent must be sign as soon as possible after inclusion.

In both cases, consent of the patient will be sought by the investigator as soon as the patient will be able to consent.

15.2 Compensation for subjects

Not applicable

15.3 Legal obligations

15.3.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in, accordance with regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and all national Laws . Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

15.3.2 Request for authorisation

Prior to starting to the study, AP-HP, as sponsor, must obtain authorisation from the Competent Authority and the Research Committee for this a clinical trial on medicinal product for human use, within the scope of its authority and in accordance with in force legislation and regulatory requirements

's authority and in accordance with in force legislation and regulatory requirements.

15.3.3 Procedures relating to data protection regulations

The computer file used for this clinical trial is implemented in accordance with French (amended “Informatique et Libertés” law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

15.3.4 Request for approval from the CNIL

For France:
Reference Method, the sponsor must obtain approval from the CNIL, because of emergency situation in accordance with Article L.1122-1-2 can be carried out in the case where the patient could not consent and family members/trustworthy person is not be present.

15.3.5 Start of the Clinical Trial

The sponsor shall notify each Member State concerned of the start of a clinical trial and the start of the recruitment through the EU portal. That notification shall be made within 15 days from the start of the clinical trial.

15.3.6 Amendments to the clinical trial

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to starting the study, approval from the CPP (Ethics Committee) and authorisation from the COMPETENT AUTHORITY within the scope of their respective authorities.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

15.3.7 End of the Clinical Trial

The end of the Clinical Trial corresponds to the end of the participation of the last person who participate to the Clinical Investigation *[to be defined otherwise if this is not the case].*
The end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified in CTIS. That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.

15.3.8 Summary of the results of the clinical trial

According to article 37.4 of the European regulation n°536/2014, irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the CTIS a summary of the results of the clinical trial. This summary shall be accompanied by a summary written in a manner that is understandable to laypersons.

15.3.9 Archiving

Specific documents for a clinical trial a medicinal product for human use will be archived by the investigator and the sponsor for 25 years after the end of the clinical trial.
This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor, containing one copy of all information notes and consent forms signed by all individuals at the site who participated in the clinical trial;
- "Study" binders for the Investigator and the sponsor, containing:
  - the successive versions of the protocol (identified by the version no. and date), and any appendices
  - the COMPETENT AUTHORITY authorisations and (Ethics Committee decisions
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the clinical trial
  - final study report
- The data collection documents

16 FUNDING AND INSURANCE

16.1 Sources of funding for the trial

PHRC-K18-102

16.2 Insurance

Pursuant to Article L.1121-10 of the Code de la Santé Publique (French Public Health Code), insurance policies must guarantee the civil liability of the sponsor and that of any contributor and cover pecuniary consequences of damages arising from the study involving human participants.

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article 76(1) of regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

17 PUBLICATION

17.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
*- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France*

17.2 Mention of the AP-HP manager (DRCI) in the acknowledgements of the text

- "The sponsor was *Assistance Publique – Hôpitaux de Paris* (Clinical Research and Innovation Delegation)"

17.3 Mention of the *financial backer* in the acknowledgements of the text

- *"The study was funded by a grant from Programme Hospitalier de Recherche Clinique – PHRC-K18-102 (Ministry of Health and Institut National du Cancer (INCA))"*

This study is registered on the website http://clinicaltrials.gov

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19 LIST OF ADDENDA

19.1 List of Investigators

Équipe *Team*	**Nom** *Name*	**Spécialité** *Specialty*	**Etablissement de santé** *Health institution*	**Téléphone / e-mail** *Phone / e-mail*	**Affiliation éventuelle à un organisme de cherche (INSERM CNRS …)** *Affiliation to clinical trial organism*
Équipe 1 (équipe de coordination) *Team 1 (coordination team)*	**Investigateur Coordonnateur** *Coordinator* ***Michael Darmon***	Intensive Care	Saint-Louis University Hospital Paris, France	+33 1 42 49 94 22 michael.darmon@aphp.fr	INSERM ECSTRA team, Biostatistics and clinical epidemiology, UMR 1153 (centre of epidemiology and biochevretic Sorbonne Paris Cité, CRESS),
	Méthodologiste *Methodologist* ***Sylvie Chevret***	Biostat	Saint-Louis University Hospital, Paris, France	0142499742 sylvie.chevret@paris7.jussieu.fr	INSERM ECSTRA team, Biostatistics and clinical epidemiology, UMR 1153 (centre of epidemiology and biostatistic Sorbonne Paris Cité, CRESS),
Équipe 2 *Team 2*	**Responsable** *Head* ***Djamel Mokart***	ICU	CLCC Institut Paoli-Calmette, Marseille France	04 91 22 33 33 MOKARTD@ipc.unicancer.fr	

Équipe 3 *Team 3*	**Responsable** *Head* **B Claire DUPUIS**	ICU	CHU Clermont-Ferrand, Clermont-Ferrand, France	04 73 75 49 82 Bcdupuis1@chu-clermontferrand.fr	
Équipe 4 *Team 4*	**Responsable** *Head* ***Kada Klouche***	ICU	CHU de Montpellier, Montpellier, France	04 67 33 67 33 k-klouche@chu-montpellier.fr	
Équipe 5 *Team 5*	**Responsable** *Head* ***Maxens DECAVELE***	ICU	CHU Pitié-Salpêtrière, Paris, France	01 42 16 77 61 maxens.decavele@aphp.fr01 42 16 00 00 alexandre.demoule@aphp.fr	
Équipe 6 *Team 6*	**Responsable** *Head* ***Pierre Perez***	ICU	CHU Nancy Nancy, France	03 83 85 85 85 p.perez@chru-nancy.fr	
Équipe 7 *Team 7*	**Responsable** *Head* ***S Anne Sophie MOREAU***	ICU	CHRU Lille Lille, France	03 20 44 40 84 sanne-sophie.moreau@chru-lille.fr	
Équipe 8 *Team 8*	**Responsable** *Head* ***M Guillaume THIERY***	ICU	CHU de Saint-Etienne	4 77 12 78 53 guillaume.thiery @chu-st-etienne.fr	
Équipe 9 *Team 9*	**Responsable** *Head* ***Laurent Argaud***	ICU	CHU Edouard Herriot, Lyon, France	04 72 11 00 15 laurent.argaud@chu-lyon.fr	
Équipe 10 *Team 10*	**Responsable** *Head* ***Guillaume Lacave***	ICU	CH de Versailles Versailles, France	01 39 63 91 33 glacave@ch-versailles	
Équipe 12 *Team 12*	**Responsable** *Head* ***Achille Kouatchet***	ICU	CHU d'Angers, Angers, France	02 41 35 36 37 ackouatchet@chu-angers.fr	
Équipe 13 *Team 13*	**Responsable** *Head* ***Frédéric Pène***	ICU	CHU Cochin, Paris, France	01 58 41 41 41 Frederic.pene@aphp.fr	
Équipe 14 *Team 14*	**Responsable** *Head* ***Thomas URBINA***	ICU	CHU Saint-Antoine, Paris, France	01 71 97 02 30 tomas.urbina@aphp.fr	

19.2 Serious Adverse Events report form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)
Il est possible de transmettre les formulaires de notification d'EIG au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons.

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche

Acronyme : Combination-Lock01

Code de la Recherche : APHP180690

Risque : D

Date de notification : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Date de prise de connaissance de l'EIG par l'investigateur : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Titre complet de la recherche :
Influence de la bithérapie antibiotique par aminosides et de l'isolement protecteur sur le devenir des patients neutropéniques admis en réanimation avec un sepsis : étude randomisée double plan factoriel

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : ..... Fax : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance :
|__|__| |__|__| |__|__|__|__|
jj mm aaaa

Age : |__|__|__|ans

Date de signature du consentement : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
.....
.....
.....
.....
.....
.....
.....

Date d'inclusion /randomisation : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

☐ Groupe avec aminoside systématique + isolement protecteur (isolement complet)
☐ Groupe avec aminoside systématique + absence d'isolement protecteur (mesures universelles uniquement)
☐ Groupe sans aminoside + isolement protecteur (isolement complet)
☐ Groupe sans aminoside + absence d'isolement protecteur (mesures universelles uniquement)

4. Médicament(s) expérimental(aux) (ME) ou produit(s) assimilé(s) [préciser le(s)quel(s)] avant la survenue de l'EIG

(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
Amikacine ☐ non applicable	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

Acronyme : Combination-Lock01

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

5. Procédures et actes ajoutés par la recherche ***(ex. : biopsies, IRM …)*** ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
Isolement protecteur (isolement complet) : ☐ oui (*renseigner la date de réalisation*) ☐ non applicable (*mesures universelles uniquement*)	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

6. Médicament(s) <u>concomitant(s)</u> au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable ***(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)***

➪ **Annexe jointe au présent formulaire :** ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours (2)	Indication	***Action prise*** *0 : poursuite sans modification de la posologie 1 : arrêt 2 : diminution de la posologie 3 : augmentation de la posologie 4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament 1 : lié au médicament 2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

Acronyme : Combination-Lock01

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

7. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire

.....

.....

.....

Organe(s) concerné(s) :

.....

.....

.....

.....

.....

.....

Date de survenue des premiers symptômes : |__|__| |__|__| |_2_|_0_|__|__|

Préciser lesquels :

.....

Date d'apparition de l'EIG :

|__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Heure de survenue : |__||__| hh |__||__| min

☐ *donnée manquante*

Délai entre la date de la dernière administration du ME/produit assimilé ou la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG :

|__||__| / |__||__| |__||__|
jj hh min

Critères de gravité :

☐ Nécessite ou prolonge l'hospitalisation :

du |__|__| |__|__| |_2_|_0_|__|__|

au |__|__| |__|__| |_2_|_0_|__|__| ☐ *en cours*

☐ Décès
☐ Mise en jeu du pronostic vital
☐ Incapacité ou handicap important ou durable
☐ Anomalie ou malformation congénitale
☐ Autre(s) critère(s) médicalement significatif(s), préciser :

.....

.....

Degré de sévérité :
☐ Léger ☐ Modéré ☐ Sévère

L'évènement a-t-il conduit à :

☐ aucune mesure prise concernant le ME ou procédure d'isolement
☐ diminution de la posologie du ME ☐ augmentation de la posologie du ME
☐ arrêt définitif du ME ou de la procédure d'isolement
☐ arrêt transitoire du ME ou de la procédure d'isolement, date de reprise : |__|__| |__|__| |_2_|_0_|__|__|
☐ ne sais pas

Récidive de l'EIG après ré-administration : ○ Non ○ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
○ Non applicable

Des mesures symptomatiques ont-elles été prises ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__| Préciser : .....

L'évènement a-t-il conduit à une levée d'insu ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__| ☐ Non applicable

L'évènement fait-il suite à :

- une erreur médicamenteuse ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- un surdosage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- un mésusage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- autre (préciser) :	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|

Evolution de l'événement

☐ **Décès**
○ sans relation avec l'EIG
○ en relation avec l'EIG
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

☐ **Sujet non encore rétabli**, préciser :
○ Etat stable ○ Amélioration ○ Aggravation

☐ **Résolu :**
○ sans séquelles
○ avec séquelles, préciser lesquelles :
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
|__|__| |__|__|
hh min

☐ **Evolution inconnue**

8. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : .....

.....

.....

9. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés].....

.....

.....

PARTIE RÉSERVÉE AU PROMOTEUR
RÉFÉRENCE VIGILANCE :

Référence GED : REC-DTYP-0192

Acronyme : Combination-Lock01

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

10. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

Lié à la recherche :

☐ **Oui :** ☐ **au(x) médicament(s)/produit(s) assimilé(s) de la recherche : le(s)quel(s) ?**
☐ **Amikacine** ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

☐ **à la (aux) procédure(s)/acte(s) de la recherche : la/le(s)quel(les) ?**
☐ **Absence d'isolement protecteur (mesures universelles uniquement)** ☐**Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

☐ **Non :** ☐ **à la progression de la maladie faisant l'objet de la recherche : Sepsis**
☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : ……**
☐ **à une maladie intercurrente, laquelle : ……**
☐ **autre, préciser : ……**

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature	Nom : Signature	

19.3 PREGNANCY NOTIFICATION FORM

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Notification et suivi d'une grossesse apparue au cours d'une recherche portant sur un Médicament ou produit assimilé***	**PARTIE RÉSERVÉE AU PROMOTEUR** **RÉFÉRENCE INTERNE :** Référence GED : REC-DTYP-0185

Ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre ce formulaire au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons.

1. Identification de la recherche

Acronyme : **Combination-Lock01**
Code de la recherche : **APHP180690**

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de la grossesse par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la Recherche :
Influence de la bithérapie antibiotique par aminosides et de l'isolement protecteur sur le devenir des patients neutropéniques admis en réanimation avec un sepsis : étude randomisée double plan factoriel

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : Fax :

3. Identification de la personne présentant une grossesse

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__| (n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Date de naissance : |__|__| |__|__| |___|___|__|__|

Date d'inclusion /randomisation : |__|__| |__|__| |2|0|__|__|

Groupe de randomisation :

☐ Groupe avec aminoside systématique + isolement protecteur (isolement complet)
☐ Groupe avec aminoside systématique + absence d'isolement protecteur (mesures universelles uniquement)
☐ Groupe sans aminoside + isolement protecteur (isolement complet)
☐ Groupe sans aminoside + absence d'isolement protecteur (mesures universelles uniquement)

Date des dernières règles : |__|__| |__|__| |2|0|__|__|
Et/ou date début de grossesse : |__|__| |__|__| |2|0|__|__|

Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__| (n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Date de naissance : |__|__| |__|__| |___|___|__|__|

Date d'inclusion /randomisation : |__|__| |__|__| |2|0|__|__|

Groupe de randomisation :

☐ Groupe avec aminoside systématique + isolement protecteur (isolement complet)
☐ Groupe avec aminoside systématique + absence d'isolement protecteur (mesures universelles uniquement)
☐ Groupe sans aminoside + isolement protecteur (isolement complet)
☐ Groupe sans aminoside + absence d'isolement protecteur (mesures universelles uniquement)

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux :	**Chirurgicaux :**

Obstétricaux : |__|__| geste |__|__| pare

Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable).*

5. Médicament(s) expérimental (aux) administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
Amikacine ☐ non applicable	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

6. Procédures et actes ajoutés par la recherche ***(Barrez l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
Isolement protecteur (isolement complet) : ☐ oui (*renseigner la date de réalisation*) ☐ non applicable (*mesures universelles uniquement*)	|__|__| |__|__| |_2_|_0_|__|__|		

Acronyme : Combination-Lock01

PARTIE RÉSERVÉE AU PROMOTEUR
RÉFÉRENCE INTERNE :
REC-DTYP-0192

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

7. Médicament(s) concomitants administré(s) dans le cadre du soin
(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ ***Oui*** ☐ ***Non applicable)***

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

8. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

9. Grossesse en cours ou issue de la grossesse ☐ (faxer un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale) ☐ (compléter ci-dessous)

Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J

☐ Fausse couche
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Grossesse extra-utérine
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Interruption de grossesse → Raison :
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :
Souffrance fœtale : ☐ Non ☐ Oui, précisez :
Mort-né : ☐ Non ☐ Oui, précisez :
Placenta normal : ☐ Oui ☐ Non, précisez :
Liquide amniotique : ☐ Clair ☐ Autre, précisez :
Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

10. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et le faxer)

Sexe : ☐ Masculin ☐ Féminin

Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm

APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____

Malformation(s) congénitale(s) : ☐ Non ☐ Oui, précisez :

Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :

Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez : ☐ Non applicable

Notificateur	Investigateur	Tampon du service :
Nom et fonction : Signature :	Nom : Signature :	

19.3 Include the SCP

The SCP is available at the following address: https://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=68502148&typedoc=R

19.4 Study design