SKin and soft tissue necrotizing INfections in the Intensive Care Unit: a prospective multi-national cohort study
SKIN-ICU

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1. Summary

Title	SKin and soft tissue necrotizing INfections in the Intensive Care Unit: a prospective multi-national cohort study
Short title	SKIN-ICU
Primary investigator	Nicolas de Prost, MD, PhD. Medical Intensive Care Unit, Henri Mondor Hospital, Créteil, France and Groupe de Recherche Clinique CARMAS, Université Paris Est Créteil, Créteil, France
Sponsor	Assistance Publique – Hôpitaux de Paris
Background	Necrotizing soft-tissue infections (NSTI) are rare and life-threatening bacterial infections characterized by subcutaneous tissue, fascia or muscle necrosis. Few prospective studies have been performed and our current knowledge on NSTI is mostly derived from retrospective single center studies. The "SKin and soft tissue necrotizing INfections in the ICU" (SKIN-ICU) study is a multinational prospective non-interventional cohort study that will include patients admitted to the ICU/intermediate care unit for NSTI or not.
Design	Multinational, prospective, standard care data collection, study not involving human subjects (in reference to article L1121-1 code de la santé publique France)
Objectives	1) To assess hospital (*i.e.,* ICU and hospital mortality) and medium-term (day-90 mortality, functional outcomes and health-related quality of life scores, HR-QoL) outcomes 2) To report the clinical presentation and microbiological epidemiology of NSTI and identify independent prognostic factors of mortality and altered quality of life
Endpoints	• Primary outcome measure: mortality at day 90 • Secondary outcome measures: o o Functional outcomes and HR-QoL at day 90; o Microorganisms involved (species, antibiogram, resistance and "difficult to treat" status); o Clinical presentation o Skin grafting and amputation
Study duration	21 months (inclusion period: 18 months + follow-up: three months)
Inclusion criteria	Age > 18 years Patient with surgically-confirmed NSTI (i.e., macroscopic appearance of tissue during surgery revealing swollen, dull gray tissues with a thin, brownish exudate with or without necrosis)
Non-inclusion criteria	Patient deprived of liberty by judicial or administrative decision or patient under guardianship expressed opposition to project's participation at the project

2. Introduction

Necrotizing soft-tissue infections (NSTI) are rare and life-threatening bacterial infections characterized by subcutaneous tissue, fascia or muscle necrosis. The mortality of NSTIs is high, ranging from 9% in non-selected patients to up to 30% in the most severe forms requiring intensive care unit (ICU) admission [1–3].

With an incidence of 4/100 000 persons per year [4], initial misdiagnosis is frequent [5], with no reliable diagnostic test available, frequently leading to a delayed surgical debridement of infected tissues, one of the main modifiable prognostic factors [6, 7]. According to international recommendations, any cutaneous infection associated with the failure of one or more organs or showing a dramatic deterioration must include the diagnosis of NSTI for consideration, even if there is no local sign of the condition being severe [8]. The diagnosis is confirmed by identifying during surgery deficient tissue, sometimes necrotic, which comes away easily in the fingers and by the presence of the typical, foul-smelling "dishwasher" exudate. The surgeon will notice necrosis of the dermis and hypodermis, which may be isolated or associated with necrosis of the fascia or even the muscle.

The early management of NSTIs is challenging and requires a coordinated and multidisciplinary approach [2, 3, 9, 10]. Treatment of NSTIs consists of early broad-spectrum antimicrobial therapy together with emergency and aggressive surgical debridement including excision of all necrotic and infected tissues [8, 9]. Few prospective studies have been performed and our current knowledge on NSTI is mostly derived from retrospective single center studies [11]. Moreover the few randomized therapeutic trials testing interventions in this setting have been disappointing, in part because of the difficulty to identify subgroups for individualized treatments [12]. Indeed, one recent study including patients from four Scandinavian centers highlighted the heterogeneity of NSTIs regarding clinical presentation, infectious localization, microbiological findings and outcomes [13]. A large international study aimed at collecting granular data on the clinical presentation, microbiology, management and outcomes of patients with NSTI admitted in the ICU and involving a large number of centers and countries is thus desirable to improve our knowledge on this devastating condition.

The "SKin and soft tissue INfections in the ICU" (SKIN-ICU) study is a multinational prospective non-interventional cohort study that will include patients with NSTI admitted or not to the ICU/intermediate care unit and aim at addressing the following points: 1) Hospital (*i.e.*, ICU and hospital mortality) and medium-term outcomes (three- and six-month survival, functional outcomes and health-related quality of life scores, HR-QoL); and 2) Clinical presentation and microbiological epidemiology of NSTI.

3. Objectives and outcome measures

3.1. Objectives

The main objectives of the SKIN-ICU study are as follows:

- To assess hospital (*i.e.*, ICU and hospital mortality) and medium-term (*i.e.*, three-month survival, functional outcomes and health-related quality of life, HR-QoL) outcomes;
- To describe the clinical presentation and microbiological epidemiology of NSTIs;

3.2. Study endpoints

- **Primary outcome measure:** mortality at day 90
- **Secondary outcome measures:**
    - Functional outcomes and HR-QoL at day 90;
    - Microorganisms involved (species, antibiogram, resistance and "difficult to treat" status);
    - Clinical presentation
    - Skin grafting and amputation

4. Methods

Multinational, prospective, standard care data collection, study not involving human subjects (in reference to article L1121-1 code de la santé publique France)

4.1. Inclusion criteria

Eligible patients will be included if they meet the following criteria:

- Age ≥ 18 years
- Patient with surgically-confirmed NSTI (i.e., macroscopic appearance of tissues during surgery revealing swollen, dull gray tissues with a thin, brownish exudate with or without necrosis)

4.2. Exclusion criteria

- Patient deprived of liberty by judicial or administrative decision or patient under guardianship
- Expressed opposition to project's participation by patient or its relative

4.3. Duration of the study

Eighteen consecutive months or 10 consecutive patients with NSTI per participating ICU, whichever occurs first. Inclusions beyond 18 months or for more than 10 patients is possible on request of the

participating ICU or Country Coordinator. A flexible start of the inclusion period will be allowed for each centre to facilitate participation in the study. Bases on our sample size calculation, the inclusion of 1033 patients will be required (see paragraph 8.1. for justification).

4.4. Data collection

The following data will be prospectively collected into a **password-protected** and **secured web-based server** (REDCap system; see **appendix 1** for an accurate definition of all collected variables):

- Center data:
    - Type of hospital/ICU/recruitment
    - Written protocol for managing NSTI
    - Infectious diseases specialist / Dermatologist availability
    - Surgical specialty involved in NSTI patients management, surgeon available 24/7 or not
- Demographics, size and weight, previous medical history, including major comorbidities
- Hospital admission data, including:
    - Description of organ failures and organ supports (*i.e.*, mechanical ventilation, vasopressors, renal replacement therapy)
    - ICU severity scores (SAPS II and SOFA)
    - NSTI characteristics: anatomic location (limbs upper or lower, abdomino-perineal, neck/head, other), portal of entry, body surface area involved (Wallace rule of nine), periarticular/circonferential involvement, local cutaneous signs, time between first symptoms and admission, NSAID exposure, imaging performed (CT scan, MRI, other)
    - Microbiological data (including type of sample (tissue, blood culture, cutaneous biopsy or subcutaneous punction aspiration), techniques used (culture, PCR, …), results, antibiotic resistance patterns), group A streptococcal colonization if searched for
- Therapeutic interventions during hospital stay, including:
    - Surgical management: time to 1st surgery (*i.e.*, time interval between hospital admission and the first surgery), total number of surgeries performed, limb amputation, extent of skin resection (% body surface using Wallace rule of nine), articular involvement, intra-operative findings
    - Antibiotic treatments: empirical treatment (molecules used, dosage, administration methods, combined therapies), combination with clindamycin or not, antibiotic de-escalation strategy or not, total duration, plasma concentration measurements if available

  - Other aspect of management: use of intravenous immunoglobulins, hyperbaric oxygen therapy, negative pressure wound therapy, skin graft, limb amputation
- ICU admission during hospital stay
- Outcomes during the ICU and hospital stay (mortality and organ failures and support)
- Medium-term outcomes : vital status at three months post-inclusion, functional outcomes (activity of daily living scale) and HR-QoL, assessed using the EQ-5D-5L (EuroQol Research Foundation, Rotterdam, The Netherlands) [14]

5. Funding and methodological support

The primary investigator has received the 2020 ESICM NEXT Start-Up Grant from the ESICM, granting 25,000 euros for two years for conducting the SKIN-ICU study. The primary investigator (PI) of the study is adequately qualified for conducting this study, and has already led multicentre cohort studies on the prognosis of ICU patients with severe infections [12–14], with a special focus on skin and soft tissue infections [16–19]. The PI is working in a group that has published a high number of scientific articles on the topic during the past 5 years [2, 11, 20, 21]. The study has methodological (Prof F. Canoui Poitrine), and logistical support from the Public Health Department, Henri Mondor Hospital, Créteil, France. Statistical analyses will be run by an independent biostatistician/data scientist (Richard Layese).

6. Potential risks and benefits

6.1. Known potential risks

The study protocol does not introduce any specific procedure, neither diagnostic method, nor treatment or surveillance. Data will be collected from the patient's medical record, based on usual care for such patients. As such, the study does not add any risk for the patient.

6.2. Known potential benefits

Patients who will be enrolled in the study will have no direct benefit. The potential benefit of this study consists in improving the knowledge for a better medical care for similar patients in the future.

7. Premature termination or suspension of the study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the PI will promptly inform the Ethics Commitee (EC) or other local authority according to the local legislation and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination could be for instance insufficient compliance to the study protocol requirements from one or several sites. Study may resume once concerns about protocol compliance and data quality are satisfactorily addressed for the sponsor and the EC.

8. Statistical methods

8.1 Sample size

Based on an expected day-90 mortality rate of 20% (primary outcome measure), with a bilateral alpha risk of 5% and an accuracy of estimation of 2.5%, the inclusion of 984 patients would be needed to include 10 covariates for estimation of association with mortality. Considering 5% of loss of follow-up or of non-analyzable observations, **a total of 1033 patients will eventually need to be included**.
Moreover, the recent literature advocates to consider 20 events per variable in predictive variables [22, 23], therefore, considering 20% of mortality, and 1033 patients included, we estimate that 207 events will occur, leading to 196 events with the 5% of lost to follow-up assumption. Considering known (n=4: age [2, 3, 13], immunosuppression [23], delayed surgery [6, 23], clinical severity reflected by arterial lactate levels, the number of organ failures or the SOFA score [3, 6, 13]) and potential (n=4: type of treatment, microorganisms involved [13, 24], comorbidities [2, 23], NSTI location) prognosis factors, a sample size of 1033 and 207 events will enable us to build a robust predictive model with **10 covariates**, which is consistent with the numbers of potential predictors estimated *a priori*.

8.2 Statistical analysis

Analysis will be reported according to STROBE guidelines for observational cohort study. A detailed statistical analysis plan will be completed before inclusion of the last patient and published/made publically available. Analysis will be performed on the population with complete data regarding baseline factors and mortality endpoints.
Descriptive analysis of baseline clinical, microbiological and surgical characteristics will be performed: categorical data will be expressed in n (%), continuous data in mean (standard deviation, SD) or median (quartile 1 - quartile 3, Q1-Q3).

Categorical endpoints will be expressed in n (%), continuous endpoints in mean (SD) or median (Q1-Q3). Survival endpoints (mortality at 90 days) will be expressed in survival rate and displayed in Kaplan-Meier survival curves.

Primary outcome measure: The baseline characteristics of survivors at day-90 will be compared to those of non-survivors at day-90 using the Pearson Chi square and the Student T test, as appropriate. Variables associated with day-90 mortality with a p value <0.20 will be considered for inclusion into the multivariate analysis. Interactions will be checked. A multivariate logistic model will be performed for multivariate analysis. Calibration and discrimination (area under the curve) of the models will be estimated.

Secondary outcome measures: Regarding factors associated with HR-QoL, a multiple linear regression will be performed.

Exploratory analyses will be performed in order to assess the impact of therapeutic interventions (*e.g.*, time to surgery, combined empirical antibiotic treatment, duration of antibiotic treatment, hyperbaric oxygen therapy, negative pressure wound therapy *etc*.) on patient-centered outcomes. Due to the observational design, we will take into account indication bias associated with several therapeutic interventions (e.g., clindamycin, intravenous immunoglobulins, hyperbaric oxygen therapy, negative pressure wound therapy), *e.g.*, age, Group A streptococcus NSTI, center effect, location of NSTI, immunosuppression, patient severity *etc*. To this end, propensity scores assessing the probability of receiving these treatments will be built and included in the multivariate models.

9. Source documents and access to source data

9.1. Access to data

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the regulatory agencies to examine clinical records for the purposes of quality assurance reviews, audits, progress, and data validity.

9.2. Source data

Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, recorded data from automated instruments.

9.3. Data confidentiality

Participant confidentiality is strictly held in trust by the participating investigators and their staff. All medical or administrative staff with an access to the data is subject to a duty of professional secrecy. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The study monitor, other authorized representatives of the sponsor, representatives of local authorities may inspect all documents and records required to be maintained by the investigator for the participants in this study. The clinical study site will permit access to such records.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to the Data Manager and the Statistician of the study. This will not include the participant's contact or identifying information. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected.

10. Ethics / protection of human subjects

10.1. Ethical standard

The investigator will ensure that this study is conducted in full conformity with the Declaration of Helsinki, ICH E6 and National law

10.2. Ethics committee

The protocol has been approved by the Ethics committee of the French Intensive Care Society (Appendix 1). The protocol and informed consent form will be submitted in each participating country by the national coordinator to the Ethics Committee (EC) for review and approval in conformity with local existing legislation. Approval of both the protocol and the non-opposition form (if required by local authorities) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the EC before the changes are implemented to the study. All changes to the non-opposition form will be EC approved.

10.3. Non-opposition process

All participants or their closest relatives will receive a verbal explanation or, if required by local authorities, a non-opposition form in terms suited to their comprehension of the study on the study purposes, the nature of the data collected and their rights as research participants, according to the requirements of local authorities.

The non-opposition process may differ in the participating countries. The compliance to local regulation should be respected. The participants may withdraw their non-opposition at any time throughout the

course of the study, and patient's withdrawal will have no impact on the quality of care that will be provided.

11. Data handling and record keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the local primary investigator (LPI). The LPI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data will be entered into a compliant data capture system (REDCap system). The data system includes password protection and internal quality checks, to identify data that appear inconsistent, incomplete, or inaccurate.

Clinical data will be entered directly from the source documents.

Each study site should respect the local legislation and apply for an approval to a local Data Protection Authority if necessary.

Study documents should be retained for a minimum of **15 years** after the end of the study. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12. Responsibilities

12.1. Primary investigator

To design the study, coordinate all actors and take primary responsibility for the conduct of the study.

12.2. Steering committee

To design the study, including protocol, data collected and scientific protocol. To participate in the analysis of the data and preparation of the manuscript. To analyse the data, results and content of the manuscript.

12.3. National coordinators

National Coordinators (NCs) will be appointed by the Steering Committee and will have a key role in the conduction of the study in the individual countries as leaders of the project. The role/responsibilities of the NC include the following:

- Advertise the study in the individual countries and identify participating hospitals and local investigators in their country.
- Apply for regulatory approval in a national level where applicable and ensure that ethical committee (EC) approvals or waivers for all the participating hospitals in the country are in place prior to the initiation of the study. The NC will receive scanned copies of the EC approvals from all centers, will check them and report to the Primary Investigator (PI). The scanned copies of the EC approval checked by the NC will be sent altogether to the PI prior to the initiation of the study.
- Assist with the translation of the study protocol/CRF where required.
- Ensure the distribution of study material to the centers (protocol, CRF, instruction manuals etc.) and make sure that the local investigators are familiar to the study material prior to the start date.
- Ensure good communication with the participating sites in the respective country and to animate local investigators to achieve optimal recruitment and follow-up during the period of the study. During the period of database quality control (data 'cleaning') the NC should animate the individual to reply in possible queries.
- They are invited to participate in data analysis and preparation of the manuscript.

12.4. Local primary investigators

There will be one local investigator per ICU with the following role/responsibilities:

- Lead the study in their hospital.
- Communication with the NC and SC for each issue that may arise.
- Apply for ethical review where applicable in accordance with the requirements for each jurisdiction.
- Ensure accurate data collection and accurate and timely eCRF completion.
- Reply promptly to possible queries during the period of database quality control
- Maintain a patient list to match identifier codes in the database to individual patients in order to record clinical outcomes and supply any missing data points.
- Guarantee the integrity, consistency and quality of data collection and ensure that the EC approval, the patient list and the paper CRFs will be kept in a safe and locked place for the period of time set in the study protocol.

13. Publication and data sharing policy

The data and the analysis issued of this study is under responsibility of the scientific committee, which is composed by the PI, at least one representative of the sponsor and the Biostatistician or Data Manager responsible of the study.

All publications should be based on the Statistical Analysis Report, which will report all statistical analyses performed after the end of the study by an independent Biostatistician (Richard Layese).

The data and analysis of the study will not be shared without an assent of the steering committee. The principal analysis will be presented on the congress of European Society of Intensive Care Medicine (ESICM). It is possible to consider that some ancillary studies could be performed on the database or a part of it. However, the ancillary studies should be approved by the steering committee in order to insure the transparency in use of the data and to cluster some similar projects to avoid redundancies.

The authors and the order of authors of the principal publication, as well as for the ancillary publications, will be preliminarily discussed by the scientific committee. Before the publication submission, the manuscript should be validated by the scientific committee.

14. Timeline expected

- **January-August 2020:**
  - First announcement of the study
  - A team of experts constitutes the steering committee
  - National coordinators are recruited
  - Protocol and data requirements are designed
  - An e-crf is designed
  - Submission of the protocol to the Research Committee of the ESICM
  - Submission of the protocol to the Ethics Committee (France)
- **April 2021-July 2022:**
  - Ethical requirements are completed by country coordinators
  - E-crf is set-up and tested
- **November 2021**: study commencement in the first centres
- **May 2023**: end of inclusion
- **August 2023**: end of follow-up of last included patient
- **September-December 2023**: data-quality control and database closure
- **January-March 2024**: data analysis of the core epidemiological description of the database

15. Expected impact of the study

This study aims at being the largest multicentre multinational prospective cohort study on NSTI. It will help delineate the clinical presentation and provide granular data on patient-centred outcomes,

microbiology, and management of patients with NSTI. The identification of potentially modifiable prognostic factors will help design future interventional studies aimed at improving the outcome of this disease. Clinical presentation data will allow for delineating clinical phenotypes potentially associated with different outcomes and thus potentially eligible to personalized interventions. Accurate data on the functional outcomes of NSTI survivors will also be collected and help improve their long-term management.

In conclusion, a large amount of high-quality data prospectively-collected from multinational centres will allow for filling important gaps in our current knowledge on this devastating disease.

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Appendix 1: Approval form of the Ethics committee of the French Intensive Care Society

SOCIÉTÉ DE RÉANIMATION DE LANGUE FRANÇAISE
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Paris, le 16/04/2020,

Cher collègue,

Votre projet de recherche "SKin and soft tissue necrotizing INfections in the Intensive Care Unit: a prospective multi-national cohort study (étude SKIN-ICU)" référencé CE SRLF 20-22 a été évalué par deux rapporteurs et par le secrétaire de la Commission d'Ethique de la SRLF.

Après réception d'une version révisée suivant les recommandations des rapporteurs, la Commission d'Ethique donne un avis favorable à votre projet.

Pour information, je vous rappelle que l'avis de la Commission d'Ethique de la SRLF ne dispense pas des obligations légales éventuelles et qu'il reste de la responsabilité de l'investigateur et du promoteur éventuel de l'étude de se mettre en conformité avec la loi sur la recherche biomédicale et en particulier de procéder aux soumissions ou avis aux comités ou commissions légalement compétentes.

Recevez, Cher Collègue, l'assurance de nos salutations distinguées.

Dr Olivier Lesieur
Secrétaire de la Commission d'Ethique