STUDY PROTOCOL

Is TIme from adMission to surgEry an independent prognostic factor for survival of patients with gastro-intestinal perforation associated with septic shock? (TIME Trial) An Italian Intersocietary retrospective and prospective observational trial.

Protocol Number:	TT.01
Protocol version number:	TIME Trial
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Site Principal Investigators	Coordinators of Emergency Department and of Surgery and Anaestesiology units (therefore maximum nr 3 members) of each participating centre
Site Data collection:	Centers collaborators (1 member only) of each participating

INTRODUCTION

Gastro-intestinal perforation is a condition that can become life-threatening in case of appearance of systemic symptoms, sepsis-related peripheral hypoperfusion and single or multiple organ failure [1] needing a prompt intervention in Emergency Department (ED) setting. In case of abdominal infection, a surgical source-control should be performed as soon as possible according to the World Society of Emergency Surgery guidelines [2] and within 12 hours from diagnosis as stated by Surviving Sepsis Campaign of 2016 [1], together with an early goal fluid resuscitation and broad-spectrum antibiotic therapy [1].

Literature reports disagreeing data about the effect of surgical timing on mortality and postoperative outcomes: Buck et al. [3] described a 2.4 % of decreased survival every hour of surgical delay in case of perforated peptic ulcers. Other authors documented significantly longer postoperative hospital stay, greater health costs [4] and a significant increase of postoperative complication [4,5] and mortality rates [4] when surgery is delayed in high-risk patients with comorbidities or age > 65 years. Azuhata [8] described a highly significant relationship between delayed surgery and patients' survival: after 6 hours from admission to ED, patients with gastrointestinal perforation and associated septic shock don't survive to surgery.

On the opposite, a few authors didn’t find a significant impact of surgical delay on the mortality rates [6,7]. Actually, heterogeneity of patient populations, definition of sepsis and septic shock, and of endpoints is responsible to disagreeing results.

A new study with clear definition of terms and endpoints is needed to assess the role of early surgery and of severity of sepsis in patients' survival after surgery for source control.

AIM OF THE STUDY

The aim of this study is to assess the impact of delay of time between patient admission to ED and surgery for source control on 30-d mortality and postoperative outcomes in patients with gastrointestinal perforation with or without septic shock. Furthermore, we want to define the time threshold within which surgery can affect patients’ survival.

DESIGN OF THE STUDY

This is an Italian National multicenter study composed by a retrospective phase of data collection from patients of past ten years and a perspective one of next two years. Data will be analyzed by the department of Oncology of A.O.U. S. Luigi Gonzaga – Orbassano (TO).

METHODS

We will retrospectively review all consecutive patients undergoing emergency surgery for source-control of intra-abdominal infections deriving from all gastro-intestinal tract perforations, in the period from 2010 to 2019 from Italian Emergency Departments (ED). We will also conduct a study with a prospective design analyzing data of same kind of patients accessing ED in the period from January 2021 to December 2022.

Definition of sepsis and septic shock

According to the new revision of Sepsis definitions published by the European Society of Intensive Care of Medicine and the Society of Critical Care Medicine in 2016 [1], **Sepsis** is now described as life-threatening organ dysfunction caused by an inappropriate answer to infection. **Organ dysfunction** is identified as an acute change > 2 points in total SOFA score consequent to the infection.

Sepsis can be identified with: Infection documented or suspected and an increase of 2 or more in the SOFA (Sequential Organ Failure Assessment) score.

Septic shock is defined as the association of clinical sepsis to:

- persistent hypotension needing vasopressors to maintain a Mean Arterial Pressure (MAP) of 65 mmHg,

- serum values of lactates > 18 mg/dL (or 2 mmol/L) with an adequate volume resuscitation measures. (Mortality rate of these patients is superior than 40%)

Scores All participating centers will fill-out scores with clinical and laboratoristic findings with the aim to stratify patients according to clinical severity at admission in Emergency Department:

- Sequential Organ Failure Assessment (SOFA) [9]

- Emergency Surgery score (ESS) [10]

- Mannheim Peritonitis Index

- The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP®) Surgical Risk Calculator (ASS) [11]: https://riskcalculator.facs.org/RiskCalculator/

INCLUSION AND EXCLUSION CRITERIA

We include in our analysis all patients with more than 18 years old undergoing emergency surgery for gastro-intestinal perforations, with or without signs of septic shock. All patients with covered perforations or abdominal perivisceral free air bubbles treated with non- operative management or delayed surgery will be excluded. An online Case Report Form (CRF) will be filled out by every participating Italian participating center.

ENDPOINTS

Primary outcome analyzed is in-hospital Clavien-Dindo > 3 complication rate [12]. Secondary outcomes are 60-d mortality rate, total length of stay (LOS), LOS in Intensive Care Unit (ICU), days of mechanical ventilation, re-intervention rate and 30-d readmission rate.

Analyzed variables are:

- **Hospital characteristics;** teaching/non-teaching setting; I/II level ED; emergency surgery/volume x year; 24H/on-call radiology and surgery team; presence of a dedicated OR in ED;

- **Patient demographics** (gender, age, Body Mass Index (BMI) and American Society of Anaesthesiologists' (ASA) classification of Physical Health, medical history of past abdominal surgical operations and comorbidities according to Charlson Comorbidity Index (CCI) [13], mainly related to corticosteroids therapy and immunosuppressive conditions),

- **Patient management in ED**: admission date and time; Priority code at admission; time of abdominal x-Ray; time of CT-scan; Time of patient evaluation by surgeon on- call; Preoperative resuscitation management (Y/N, type, time of beginning); presence of Sepsis (infection documented or suspected + SOFA >=2) and of septic shock (sepsis + persistent hypotension needing vasopressors to maintain a Mean Arterial Pressure (MAP) of 65 mmHg; serum values of lactates > 18 mg/dL (or 2 mmol/L) with an adequate volume resuscitation measures) at admission or during patient stay in ED; SOFA score at admission; Emergency surgery score; ACS NSQIP® Surgical Risk score.

- **Radiological findings**: CT-scan reports of patients selected will be analyzed by site data-collection centers with the aim to identify typical and atypical radiological findings (subdiaphragmatic free gas, free peritoneal fluid, bowel wall discontinuity, extraluminal oral contrast, extraluminal abscess, abdominal collections, fat stranding, portal venous gas, wall bowel thickening, pneumatosis and mucosal hyperenhancement). [14]

- **Surgery:** Time of skin incision; Type and duration of surgery; source control surgery, Open Abdomen (VAC therapy); surgical approach; site and cause of perforation; pathologic data; Emergency surgery score; ACS NSQIP® Surgical Risk score.

- **Postoperative Course:** Preoperative mortality (patients die before surgery); Medical and Surgical complications (Clavien-Dindo score); total LOS; LOS in ICU; days of Mechanical Ventilation; Re-intervention rate; 90-d mortality

STUDY TIMING

- Deadline of Data collection for retrospective study: April 2021.
- Deadline of data collection for prospective study: December 2022

STATISTICS

Planned sample size

With a binary response variable, β=0·95, α=0·05, an anticipated small effect size and an allocation ratio 1:10 (Early treatment Yes vs. No), it has been calculated that 3276 patients are required to detect an association between the variables and the endpoint.

Planned Analyses

Time between patient admission to ED and surgery will be analyzed as a continuous variable with t-Student's tests, comparing means between the different outcomes (primary and secondary). Different cut-off will be tested to define a significant time threshold correlating with outcomes. If necessary, more time intervals will be evaluated to evaluate correlations between the variables collected and the time.

DATA MANAGING AND PRIVACY

Patients information will be anonymized and de-identified prior to analysis by an Excel file sent to all participants centers. Clinical data will be obtained from medical records, hospital informatics systems and prospective clinical databases.

Results will be the property of Università degli studi di Torino and of the researchers involved in the conduction of the multicenter project.

ETHICAL CONSIDERATIONS

No clinical decision for all involved patients will be influenced by this analysis, with the full compliance with the principles of ethical conduct in human research. This study will be submitted to ethics committee of AOU San Luigi Gonzaga of Orbassano (TO).

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