# SYNOPSIS

| | |
|---|---|
| **Title (acronym)** | **TIME-Trial**: **"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"** |
| **Proponent Center** | Department of Oncology of A.O.U. S. Luigi Gonzaga – Orbassano (TO) |
| **P.I.** | Prof. Maurizio Degiuli |
| **Rationale** | 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.<br><br>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].<br><br>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.<br><br>On the opposite, a few authors didn't find a significant impact of surgical delay on the mortality rates [6,7].<br><br>Actually, heterogeneity of patient populations, definition of sepsis and septic shock, and of endpoints is responsible to disagreeing results.<br><br>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. |
| **Clinical Phase** | Retrospective and prospective trial |

| | |
|---|---|
| **Objective** | 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. |
| | |
| **Study design** | This is nationwide multicentre retrospective and prospective study. |
| **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. |
| **Variables under study** | **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;<br><br>**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),<br><br>**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; Emergency surgery score; ACS NSQIP® Surgical Risk score.<br><br>**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). |

| | |
|---|---|
| | **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.<br><br>**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 |
| **End-points** | 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 |
| | |
| | |

| | |
|---|---|
| **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<br><br>are required to detect an association between the variables and the endpoint. |
| **Statistical methods** | 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. |
| **Duration of the Study** | Until 12/2022 |
| **Ethical Committee** | Protocol submitted to ethical committee of A.O.U. S. Luigi Gonzaga – Orbassano (TO) waiting for approval |
| **Main References** | [[1]. Andrew Rhodes Evans Dellinger **Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic shock: 2016** Intensive Care Medicine volume 43, pages 304- 377 (2017)<br><br>[2]. Sartelli M, Viale P, Catena F, Ansaloni L, Moore E, Malangoni M, et al. **WSES guidelines for management of intra-abdominal infections**. World J Emerg Surg. 2013;8(1):3.<br><br>[3]. Buck DL, Vester-Andersen M, Moller MH. **Surgical delay is a critical determinant of survival in perforated peptic ulcer**. Br J Surg. 2013:100(8):1045–9. |

[5]. Ong M, Guang TY, Yang TK. **Impact of surgical delay on outcomes in elderly patients undergoing emergency surgery: a single center experience**. *World J Gastrointest Surg* 2015;7:208-13.

[6]. Hecker A, Schneck E, Rohrig R, et al. **The impact of early surgical intervention in free intestinal perforation: a time-to- intervention pilot study**. World J Emerg Surg. 2015;10:54.

[7]. Vester-Andersen M, Lundstrøm LH, Buck DL, et al. **Association between surgical delay and survival in high-risk emergency abdominal surgery. A population-based Danish cohort study**. *Scand J Gastroenterol* 2016;51:121-8.

[8]. Azuhata T, Kinoshita K, Kawano D, et al. **Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock**. *Crit Care* 2014;18:R87.

[10]. Anirudh R Nandan, Jordan D Bohnen, Naveen F Sangji, Thomas Peponis, Kelsey Han, D Dante Yeh, Jarone Lee, Noelle Saillant, Marc De Moya, George C Velmahos, David C Chang, Haytham M A Kaafarani **The Emergency Surgery Score (ESS) accurately predicts the occurrence of postoperative complications in emergency surgery patients**J Trauma & Acute Care Surgery 2017 Jul;83(1):84-89.

[11].Karl Y. Bilimoria, Yaoming Liu, Jennifer L. Paruch, Lynn Zhou, Thomas E. Kmiecik, Clifford Y. Ko, Mark E. Cohen, **Development and Evaluation of the Universal ACS NSQIP Surgical Risk Calculator: A Decision Aid and Informed Consent Tool for Patients and Surgeons,** Journal of the American College of Surgeons, Volume 217, Issue 5, 2013, Pages 833-842.e3

[12]. Dindo D, Demartines N, Clavien PA. **Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey**. *Ann Surg* 2004; 240: 205-213

[13].Charlson ME, Pompei P, Ales KL, MacKenzie CR. **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation**. *J Chronic Dis* 1987; 40: 373- 383

[14].Kothari K, Friedman B, Grimaldi GM, Hines JJ.Abdom Radiol (NY) **Nontraumatic large bowel perforation: spectrum of etiologies and CT findings**.2017 Nov;42(11):2597-2608.

[4]. Zaid Al-Qurayshi, Sudesh Srivastav, Emad Kandil **Postoperative outcomes in patients with perforated bowel: early versus late intervention** J Surg Res 2016 Jun 1;203(1):75-81. Epub 2016 Mar 25.

| | |
|---|---|
| | [9]. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).** JAMA. 2016 Feb 23; 315(8):801-10.<br><br>[15]. Wacha H, Linder MM, Feldman U, Wesch G, Gundlach E, Steifensand RA. **Mannheim peritonitis index – prediction of risk of death from peritonitis: construction of a statistical and validation of an empirically based index.** Theoretical Surg. 1987;1:169–77. |
| | |
| | |
| | |