

# Early on-demand drainage versus standard management among acute necrotizing pancreatitis patients complicated by persistent organ failure

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| <b>Submission date</b><br>17/10/2019   | <b>Recruitment status</b><br>No longer recruiting | <input type="checkbox"/> Prospectively registered<br><input type="checkbox"/> Protocol                       |
| <b>Registration date</b><br>21/10/2019 | <b>Overall study status</b><br>Completed          | <input type="checkbox"/> Statistical analysis plan<br><input type="checkbox"/> Results                       |
| <b>Last Edited</b><br>18/06/2020       | <b>Condition category</b><br>Digestive System     | <input type="checkbox"/> Individual participant data<br><input type="checkbox"/> Record updated in last year |

## Plain English summary of protocol

### Background and study aims

Sometimes people with severe acute pancreatitis can develop a complication where the pancreas loses its blood supply. This can cause some of the tissue of the pancreas to die (necrosis). When this happens, the pancreas can become infected, which can spread into the blood (sepsis) and cause organ failure. People with necrosis and an infection may need injections of antibiotics and surgery to remove the dead tissue. This is a very serious complication that needs treating, and it can be fatal. The study aims to compare standard treatment with a standard treatment preceded by fluid drainage immediately upon diagnosis.

### Who can participate?

All adult patients admitted with a primary diagnosis of acute pancreatitis and persistent organ failure to one of the five participating hospitals of the Chinese Acute Pancreatitis Clinical Trials Group will be assessed for eligibility on a daily basis during their hospital stay.

### What does the study involve?

Patients will be randomised to receive either immediate drainage followed by standard treatment, or standard treatment.

### What are the possible benefits and risks of participating?

Participants can get some clinical benefit from the trial and some advice from doctors

### Where is the study run from?

1. Jinling Hospital affiliated to Nanjing University (the lead center)
2. The First Affiliated Hospital of Nanchang University
3. Xiang Ya hospital Zhongnan University
4. Sir Run Run Shaw Hospital affiliated with the Zhejiang University School of Medicine
5. Xijin Hospital, of the Fourth Military Medical University

When is the study starting and how long is it expected to run for?

March 2019 March 2022

Who is funding the study?

Jiangsu Province Key Research and Development Program (Social Development) Project

Who is the main contact?

1. Dr Qu Cheng

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**Study website**

<https://capctg.medit.cn/>

## Contact information

**Type(s)**

Public

**Contact name**

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## Additional identifiers

**EudraCT/CTIS number**

Nil known

**IRAS number**

**ClinicalTrials.gov number**

Nil known

**Secondary identifying numbers**

2018NZKY-009-04

## Study information

**Scientific Title**

Early on-demand drainage versus standard management among acute necrotizing pancreatitis patients complicated by persistent organ failure: an open-label multicenter randomized controlled trial

## **Acronym**

TIMING

## **Study objectives**

Current study hypothesis as of 18/06/2020:

Early percutaneous drainage in selected patients with acute necrotizing pancreatitis (ANC) and persistent organ failure (POF), who have aggravating or long-lasting organ failure during week 2-3 will result in improved clinical outcomes. We called this an on-demand approach for short. This will be tested in this randomized, controlled, multi-center study, aiming to compare the effect of the early on-demand drainage of ANC and standard treatment (delayed intervention).

Previous study hypothesis:

Early percutaneous drainage in selected patients with acute necrotizing pancreatitis (ANC) and persistent organ failure (POF), who have aggravating or long-lasting organ failure during week 2-3 will result in improved clinical outcomes. We called this an on-demand approach for short. This will be tested in this randomized, controlled, multi-center study, aiming to compare the effect of the early on-demand intervention of ANC and standard treatment (delayed intervention)

## **Ethics approval required**

Old ethics approval format

## **Ethics approval(s)**

Current ethics approval as of 18/06/2020:

Approved 29/11/2018, Clinical trial ethics committee of the Jinling hospital (305 Zhongshan Road East, Nanjing, Jiangsu, China; wuqiong80863234@163.com; +861 (0)25-80863234), ref: 2018NZKY-009-04

Previous ethics approval:

Approved 29/11/2018, Clinical trial ethics committee of the General Hospital of the Eastern Theater (305 Zhongshan Road East, Nanjing, Jiangsu, China; wuqiong80863234@163.com; +861 (0)25-80863234), ref: 2018NZKY-009-04

## **Study design**

Multi-center randomized controlled open-label trial

## **Primary study design**

Interventional

## **Secondary study design**

Randomised controlled trial

## **Study setting(s)**

Hospital

## **Study type(s)**

Treatment

## **Participant information sheet**

No participant information sheet available

## **Health condition(s) or problem(s) studied**

Acute pancreatitis

## **Interventions**

Current interventions as of 18/06/2020:

This randomized, controlled, multi-center study, aims to compare the effect of the early on-demand drainage of ANC and standard treatment (delayed intervention)

Early on-demand PCD group (the EOD group):

In addition to the standard treatment, ultrasound or computed tomography(CT) guided PCD will be performed within 24 hours of randomization. Early on demand endoscopic drainage is not permitted in this arm, as we can not monitor daily volume of the endoscopic drain. At least one drainage catheter with size from 12F to 16F will be placed to drain the ANC, and the content drained from the site will be cultured to determine whether it is sterile or infected. More drains are permitted if deemed clinically necessary based on patient status and extent of the collection. The treating physician is responsible for choosing the access routes, size, and the number of drains. The percutaneous drains will be audited every day and removed to reduce the unnecessary risk for introducing infection when the volume of a given catheter is less than 50ml (including 50ml) for three consecutive days and infection has not been suspected or confirmed. Debridement of the infected necrosis (necrosectomy) will be performed once there is encapsulation and as scheduled by the treating physician. For minimally-invasive techniques, both percutaneous and endoscopic necrosectomy are acceptable based on the technical preference and availability within each participating center.

Standard-care group (the standard group):

No intervention will be immediately applied if the participant is randomized to this group unless meeting the "rescue intervention criteria" shown below. Interventions, including PCD and necrosectomy, will be delayed until high suspicion or diagnosis of infection associated with WON and preferably at least four weeks following admission. Both percutaneous drainage and endoscopic transluminal drainage can be selected for the initial step, and necrosectomy would be undertaken when necessary.

Previous interventions:

This randomized, controlled, multi-center study, aims to compare the effect of the early on-demand intervention of ANC and standard treatment (delayed intervention)

Early intervention:

In addition to the standard treatment, ultrasound or CT guided percutaneous drainage would be applied within 24 hours once the patient is randomized to this group. At least one drainage catheter with size from 12F to 16F should be placed to drain the ANC, the content drained from the site will be tested by the standard procedure to detect potential infection (more drains are permitted). The treating physician is responsible for choosing the access routes, size and number of catheters.

Standard-treatment:

No intervention would be immediately applied if the participant is randomized to this group.

Interventions including catheter drainage and necrosectomy would be delayed until suspicion or diagnosis of pancreatic infection and preferably after encapsulation of the necrotic collection (after four weeks for the best).

Patients will be randomly allocated to receive early intervention, within 24 hours after randomization, or standard treatment (delayed strategy) according to the current guidelines. Patients are randomized (1:1 ratio within each participating center and sample size of each center was predefined based on its volume) with a web-based randomization module (Interactive Web-Respond System (IWRS)).

## **Intervention Type**

Procedure/Surgery

## **Primary outcome measure**

Current primary outcome measure as of 18/06/2020:

Death and/ or major complications during the index admission from randomization to hospital discharge or death. Major complications refer to new-onset organ failure (cardiovascular, renal and respiratory), bleeding requiring intervention and gastrointestinal perforation or fistula requiring intervention.

Previous primary outcome measure:

1. All-cause mortality in hospital
2. Major complications during the observational period

## **Secondary outcome measures**

Current secondary outcome measures as of 18/06/2020:

1. New-onset organ failure before the time of hospital discharge or death
2. Bleeding requiring intervention before the time of hospital discharge or death
3. Gastrointestinal perforation or fistula requiring intervention before the time of hospital discharge or death
4. Deteriorated organ failure before the time of hospital discharge or death
5. Organ failure score assessed at 14 and 21 days after randomization
6. Organ failure-free days during the 21-day period following randomization
7. Intra-abdominal pressure for seven consecutive days after randomization and 14, 21 days after randomization
8. Incidence of infected pancreatic necrosis before the time of hospital discharge or death
9. Incidence of sepsis before the time of hospital discharge or death
10. New prescription of mechanical ventilation, renal replacement therapy and vasoactive agents before the time of hospital discharge or death
11. Incidence of pancreatic fistula before the time of hospital discharge or death
12. Incidence of symptomatic splenic vein thrombosis before the time of hospital discharge or death
13. Requirement of minimally inv supraventricular tachycardia asive debridement before the time of hospital discharge or death
14. Requirement of open surgery before the time of hospital discharge or death
15. Duration of ICU admission before the time of hospital discharge or death
16. Duration of hospital admission before the time of hospital discharge or death
17. Total cost before the time of hospital discharge or death
18. Vital status on 90 days after randomization

Previous secondary outcome measures:

1. The fluctuation of organ functions reflected by the area under curve according to the revised Marshall score for seven consecutive days after randomization
2. Organ function assessed by revised Marshall at 14 and 21 days after randomization if available
3. Intraabdominal pressure for seven consecutive days after randomization and 14, 21 days after randomization if available
4. Incidence and timing of infected pancreatic necrosis
5. Incidence and timing of sepsis
6. Incidence and timing of other common complications such as abdominal bleeding and fistulas
7. Requirement of open surgery
8. ICU duration
9. Hospital duration
10. Total cost

**Overall study start date**

01/06/2016

**Completion date**

01/06/2022

## Eligibility

### Key inclusion criteria

Current inclusion criteria as of 18/06/2020:

1. Aged 18 to 70 years
2. Able to provide informed consent
3. Confirmed diagnosis of AP
4. CT diagnosis of acute necrotic collection (ANC)
5. Technically able to be drained percutaneously, by ultrasound or CT guidance
6. Confirmed persistent organ failure (either respiratory, renal and/or cardiovascular lasting for more than 48 hours) that had not resolved by Day 7
7. During Day 8-Day 21, one or more of these criteria:
  - 7.1. New-onset organ failure not present on Day 7 (no alleviation within 24 hours)
  - 7.2. Organ failure (either single or multiple, modified Marshall score or SOFA score $\geq$ 2) persist for seven natural days from Day 1
  - 7.3. Aggravation of organ failure from that on Day 7 evidenced by increased modified Marshall score or SOFA score (no alleviation within 24 hours)

Previous inclusion criteria:

Inclusion criteria for the screening period

Screening period starts from day 8 and extends to the end of the third week (day 21) consisting of 14 days:

1. Symptoms and signs of acute pancreatitis based on abdominal pain suggestive of AP, serum amylase at least three times the upper limit of normal, and/or characteristic findings of AP on computed tomography
2. Necrotic collection with available routes for ultrasound or CT guided percutaneous no matter sterile or infected
3. Confirmed persistent organ failure (either respiratory, renal or cardiovascular lasting for more than 48 hours), the organ failure score at day7 will be set as the baseline for the screening period
4. Age between 18 to 70 years old

Inclusion Criteria for randomization during screening period:

1. Patients in the screening period
2. Signs of deterioration from the baseline during the screening period including:
  - 2.1. New-onset organ failure (no alleviation within 24 hours)
  - 2.2. Unalleviated organ failure (either single or multiple, modified Marshall score $\geq$ 2) lasting for at least seven days including the duration before the screening period
  - 2.3. Aggravation of organ failure from the baseline (either single or multiple) evidence by increased modified Marshall score (no alleviation within 24 hours)

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

120

**Key exclusion criteria**

Current exclusion criteria as of 18/06/2020:

1. Pregnant pancreatitis
2. Chronic pancreatitis
3. Pancreatic tumor-related pancreatitis
4. Percutaneous or transluminal drainage or surgery is undertaken before admission
5. Patients had a history of cardio-pulmonary resuscitation during this episode
6. Patients with a known history of severe cardiovascular, respiratory, renal or hepatic disease defined as (1) greater than New York Heart Association class II heart failure, (2) active myocardial ischemia or (3) cardiovascular intervention within previous 60 days, (4) history of cirrhosis or (5) chronic kidney disease with creatinine clearance $<$  40 mL/min, or (6) chronic obstructive pulmonary disease with requirement for home oxygen

Previous exclusion criteria:

1. Pregnant
2. Chronic pancreatitis, recurrent acute pancreatitis or pancreatic tumor-related pancreatitis
3. Percutaneous or transluminal drainage or surgery undertaken before admission
4. Previous history of cardio-pulmonary resuscitation
5. History of severe cardiovascular, respiratory, renal, hepatic, hematologic, or immunologic disease defined as:
  - 5.1. Greater than New York Heart Association class II heart failure
  - 5.2. Active myocardial ischemia
  - 5.3. Cardiovascular intervention within the previous 60 days
  - 5.4. History of cirrhosis
  - 5.5 Chronic kidney disease with creatinine clearance $<$  40 mL/min
  - 5.6 Chronic obstructive pulmonary disease with requirement for home oxygen

**Date of first enrolment**

01/03/2019

**Date of final enrolment**

01/03/2022

## **Locations**

**Countries of recruitment**

China

**Study participating centre**

**Jinling Hospital affiliated to Nanjing University**

305 Zhongshan Road East

Nanjing

China

210000

**Study participating centre**

**The First Affiliated Hospital of Nanchang University**

17 Yongwaizheng street

Nanchang

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330000

**Study participating centre**

**Xiang Ya hospital Zhongnan University**

87 Xiangya Road

Changsha

China

410000

**Study participating centre**

**Sir Run Run Shaw Hospital affiliated with the Zhejiang University School of Medicine**

3 Qingchun East Road

Jiangan District

Hangzhou

China

310000

**Study participating centre**



**Xijin Hospital of the Fourth Military Medical University**  
127 Changle West Road  
Xincheng District  
Xi'an City  
Xian  
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## Sponsor information

### Organisation

Department of science and technology of Jiangsu province

### Sponsor details

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### Sponsor type

Government

### ROR

<https://ror.org/02mkqta53>

## Funder(s)

### Funder type

Government

### Funder Name

Jiangsu Province Key Research and Development Program (Social Development) Project  
(BE2016749)

## Results and Publications

### Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal.

### Intention to publish date

01/06/2023

### **Individual participant data (IPD) sharing plan**

All data generated or analysed during this study will be included in the subsequent results publication

### **IPD sharing plan summary**

Other