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Hua C, Bosc R, Sbidian E, De Prost N, Hughes C, Jabre P, Chosidow O, Le Cleach L. Interventions for necrotizing soft tissue infections in adults. *Cochrane Database of Systematic Reviews* 2018, Issue 5. Art. No.: CD011680. DOI: 10.1002/14651858.CD011680.pub2.

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#### [Intervention Review]

# Interventions for necrotizing soft tissue infections in adults

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Editorial group: Cochrane Skin Group.

Publication status and date: New, published in Issue 5, 2018.

**Citation:** Hua C, Bosc R, Sbidian E, De Prost N, Hughes C, Jabre P, Chosidow O, Le Cleach L. Interventions for necrotizing soft tissue infections in adults. *Cochrane Database of Systematic Reviews* 2018, Issue 5. Art. No.: CD011680. DOI: 10.1002/14651858.CD011680.pub2.

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#### **ABSTRACT**

# **Background**

Necrotizing soft tissue infections (NSTIs) are severe and rapidly spreading soft tissue infections of the subcutaneous tissue, fascia, or muscle, which are mostly caused by bacteria. Associated rates of mortality and morbidity are high, with the former estimated at around 23%, and disability, sequelae, and limb loss occurring in 15% of patients. Standard management includes intravenous empiric antimicrobial therapy, early surgical debridement of necrotic tissues, intensive care support, and adjuvant therapies such as intravenous immunoglobulin (IVIG).

# **Objectives**

To assess the effects of medical and surgical treatments for necrotizing soft tissue infections (NSTIs) in adults in hospital settings.

#### **Search methods**

We searched the following databases up to April 2018: the Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, and LILACS. We also searched five trials registers, pharmaceutical company trial results databases, and the US Food and Drug Administration and the European Medicines Agency websites. We checked the reference lists of included studies and reviews for further references to relevant randomised controlled trials (RCTs).

#### **Selection criteria**

RCTs conducted in hospital settings, that evaluated any medical or surgical treatment for adults with NSTI were eligible for inclusion. Eligible medical treatments included 1) comparisons between different antimicrobials or with placebo; 2) adjuvant therapies such as intravenous immunoglobulin (IGIV) therapy compared with placebo; no treatment; or other adjuvant therapies. Eligible surgical treatments included surgical debridement compared with amputation, immediate versus delayed intervention, or comparisons of number of interventions.

RCTs of hyperbaric oxygen (HBO) therapy for NSTI were ineligible because HBO is the focus of another Cochrane Review.



#### **Data collection and analysis**

We used standard methodological procedures expected by Cochrane. The primary outcome measures were 1) mortality within 30 days, and 2) proportion of participants who experience a serious adverse event. Secondary outcomes were 1) survival time, and 2) assessment of long-term morbidity. We used GRADE to assess the quality of the evidence for each outcome.

#### **Main results**

We included three trials randomising 197 participants (62% men) who had a mean age of 55 years. One trial compared two antibiotic treatments, and two trials compared adjuvant therapies with placebo. In all trials, participants concomitantly received standard interventions, such as intravenous empiric antimicrobial therapy, surgical debridement of necrotic tissues, intensive care support, and adjuvant therapies. All trials were at risk of attrition bias and one trial was not blinded.

#### Moxifloxacin versus amoxicillin-clavulanate

One trial included 54 participants who had a NSTI; it compared a third-generation quinolone, moxifloxacin, at a dose of 400 mg given once daily, against a penicillin, amoxicillin-clavulanate, at a dose of 3 g given three times daily for at least three days, followed by 1.5 g three times daily. Duration of treatment varied from 7 to 21 days. We are uncertain of the effects of these treatments on mortality within 30 days (risk ratio (RR) 3.00, 95% confidence interval (CI) 0.39 to 23.07) and serious adverse events at 28 days (RR 0.63, 95% CI 0.30 to 1.31) because the quality of the evidence is very low.

#### AB103 versus placebo

One trial of 43 randomised participants compared two doses, 0.5 mg/kg and 0.25 mg/kg, of an adjuvant drug, a CD28 antagonist receptor (AB103), with placebo. Treatment was given via infusion pump for 10 minutes before, after, or during surgery within six hours after the diagnosis of NSTI. We are uncertain of the effects of AB103 on mortality rate within 30 days (RR of 0.34, 95% CI 0.05 to 2.16) and serious adverse events measured at 28 days (RR 1.49, 95% CI 0.52 to 4.27) because the quality of the evidence is very low.

#### Intravenous immunoglobulin (IVIG) versus placebo

One trial of 100 randomised participants assessed IVIG as an adjuvant drug, given at a dose of 25 g/day, compared with placebo, given for three consecutive days. There may be no clear difference between IVIG and placebo in terms of mortality within 30 days (RR 1.17, 95% CI 0.42 to 3.23) (low-certainty evidence), nor serious adverse events experienced in the intensive care unit (ICU) (RR 0.73 CI 95% 0.32 to 1.65) (low-certainty evidence).

Serious adverse events were only described in one RCT (the IVIG versus placebo trial) and included acute kidney injury, allergic reactions, aseptic meningitis syndrome, haemolytic anaemia, thrombi, and transmissible agents.

Only one trial reported assessment of long-term morbidity, but the outcome was not defined in the way we prespecified in our protocol. The trial used the Short Form Health Survey (SF36). Data on survival time were provided upon request for the trials comparing amoxicillin-clavulanate versus moxifloxacin and IVIG versus placebo. However, even with data provided, it was not possible to perform survival analysis.

# **Authors' conclusions**

We found very little evidence on the effects of medical and surgical treatments for NSTI. We cannot draw conclusions regarding the relative effects of any of the interventions on 30-day mortality or serious adverse events due to the very low quality of the evidence.

The quality of the evidence is limited by the very small number of trials, the small sample sizes, and the risks of bias in the included trials. It is important for future trials to clearly define their inclusion criteria, which will help with the applicability of future trial results to a real-life population.

Management of NSTI participants (critically-ill participants) is complex, involving multiple interventions; thus, observational studies and prospective registries might be a better foundation for future research, which should assess empiric antimicrobial therapy, as well as surgical debridement, along with the placebo-controlled comparison of adjuvant therapy. Key outcomes to assess include mortality (in the acute phase of the condition) and long-term functional outcomes, e.g. quality of life (in the chronic phase).

### PLAIN LANGUAGE SUMMARY

# Treatments for necrotizing (i.e. destructive) soft tissue infections in adults

## What is the aim of this Cochrane Review?

We wanted to find out which medicines and surgical treatments are effective and safe for treating necrotizing soft tissue infections (NSTI). NSTI are serious infections of the tissues underneath the skin, mostly caused by bacteria.



#### **Key messages**

The available evidence from three studies is not strong enough to enable us to draw definite conclusions about the effectiveness and safety of the different treatments for NSTI assessed in this review. All studies assessed number of deaths and risk of serious side effects.

Factors affecting our confidence in the results included the following:

- the small number of trials and participants;
- weaknesses in the trial methodologies which affect the reliability of results; and
- poor definition of the participants' condition.

We found no evidence that assessed antimicrobial therapy (which targets a wide range of disease-causing bacteria and fungi) or surgical removal of damaged tissue.

In future studies, risk of death should be a key outcome in the short term (i.e. within 30 days) phase of the condition, and outcomes such as loss of work and quality of life should be assessed in the long-term phase (after 30 days).

#### What was studied in the review?

We included people with NSTI. These types of infections are rare, but can become life-threatening if left untreated, or result in amputation. NSTIs need emergency treatment, usually with antibiotics and surgical removal of the infected tissue.

We searched for studies that assessed treatments for diagnosed NSTI in hospitalised adults. This included:

- surgical treatments: surgical removal of damaged tissue compared with amputation, immediate versus delayed treatment, or comparison of a number of treatments;
- antimicrobial medicines which kill bacteria and fungi compared with placebo (i.e. an identical but inactive treatment), or each other;
- medicines given as add-on therapies in addition to the primary treatment (adjuvant therapies) compared with placebo, no treatment, or other adjuvant therapies.

Our main outcomes of interest were death within 30 days, and any serious treatment side effects.

#### What are the main results of the review?

We found three studies, which enrolled 197 adults (117 men, average age = 55). The trials were conducted worldwide, funded by pharmaceutical companies; they assessed antimicrobial therapy or treatments that control the immune system.

One study compared two antibiotics: moxifloxacin and amoxicillin-clavulanate, administered directly into a vein for seven to 21 days. It found no clear difference between the treatment groups in terms of number of deaths within 30 days, but we are uncertain about this result because it is based on very low-certainty evidence.

One study compared placebo with a new type of treatment that controls immune response (called AB103) given in a single dose (of either 0.5 mg/kg or 0.25 mg/kg), administered directly into a vein. Participants also received standard treatment for NSTI based on antibiotics and surgical treatment, so AB103 was given as an adjuvant therapy. There was no clear difference between the treatment groups in terms of number of deaths within 30 days, but we are uncertain about this conclusion because it is based on very low-certainty evidence.

One study compared injections of immunoglobulin (an antibody, part of the body's immune system) with placebo. Both treatments were given for three consecutive days. Participants also received standard treatment for NSTI based on antibiotics and surgical treatment, thus immunoglobulin was given as an adjuvant therapy. There was no clear difference between the treatment groups in terms of the number of deaths within 30 days (low-certainty evidence).

No study showed any clear difference between treatments in terms of serious side effects, but the evidence is not strong enough to confirm this. The immunoglobulin study listed the side effects encountered, which included kidney injury, allergic reactions, meningitis, blood clots, and infectious agents (low-certainty evidence).

Only one trial reported assessment of long-term illness but it was not defined as we had required in our in the protocol (the trial used another scale: the Short Form Health Survey (SF36). Survival time was reported in two trials (but not enough data were provided to analyse these results).

# How up-to-date is this review?

We searched for studies published up to April 2018.