

Clinical Commissioning Policy: Hyperbaric Oxygen Therapy for necrotising soft tissue infections (all ages)

For implementation from 1 April 2019

NHS England Reference: 170070P



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Medical	Operations and Information	Specialised Commissioning
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

Publications Gateway Reference: 07603

Document Purpose	Policy
Document Name	Clinical Commissioning Policy: Hyperbaric Oxygen Therapy for necrotising soft tissue infections (all ages)
Author	Specialised Commissioning Team
Publication Date	20 July 2018
Target Audience	CCG Clinical Leaders, Care Trust CEs, Foundation Trust CEs , Medical Directors, Directors of PH, Directors of Nursing, NHS England Regional Directors, NHS England Directors of Commissioning Operations, Directors of Finance, NHS Trust CEs
Additional Circulation List	
Description	Not for routine commissioning
Cross Reference	
Superseded Docs (if applicable)	
Action Required	
Timing / Deadlines (if applicable)	
Contact Details for further information	england.specialisedcommissioning@nhs.net

Document Status

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Clinical Commissioning Policy: Hyperbaric Oxygen Therapy for necrotising soft tissue infections (all ages)

First published: July 2018

**Prepared by NHS England Specialised Services Clinical Reference Group for
Hyperbaric Oxygen Therapy**

Published by NHS England, in electronic format only.

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Policy Statement

NHS England will not routinely commission hyperbaric oxygen therapy for necrotising soft tissue infections in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain Language Summary

About necrotising soft tissue infection

Necrotising soft tissue infection (NSTI) is a rare but serious bacterial infection that affects the tissue beneath the skin, and surrounding muscles and organs (NHS Choices, 2016). It is sometimes called the "flesh-eating disease", although the bacteria that cause it don't "eat" flesh – they release toxins that damage nearby tissue (NHS Choices, 2016). Necrotising fasciitis can start from a relatively minor injury, such as a small cut, but gets worse very quickly and can be life-threatening if it is not recognised and treated early on (NHS Choices, 2016).

About current treatments

NSTI needs to be treated in hospital.

The main treatments are:

- **surgery to remove infected tissue** – this may be repeated several times to ensure all the infected tissue is removed, and occasionally it may be necessary to amputate affected limbs
- **antibiotics** – usually several different types are given directly into a vein
- **supportive treatment** – including treatment to control blood pressure, fluid levels and organ functions

People with the condition will often need to be looked after in an intensive care unit and may need to stay in hospital for several weeks. While in hospital, they may be isolated from other patients to reduce the risk of spreading the infection (NHS Choices, 2016).

About the new treatment

Hyperbaric oxygen therapy (HBOT) has been suggested as an adjuvant treatment (another treatment used together with the primary treatment) of NSTIs. HBOT is delivered by giving a patient oxygen to breathe while in a pressurised chamber so that a higher level of oxygen can be dissolved in the patient's blood plasma. Inhaling oxygen at increased pressure is intended to improve oxygen supply to the infected

tissue. During HBOT, the patient is in a pressure chamber, usually for 45 to 120 minutes at least once daily.

What we have decided

NHS England has carefully reviewed the evidence to treat necrotising soft tissue infection with hyperbaric oxygen therapy. We have concluded that there is not enough evidence to make the treatment available at this time.

1 Introduction

About necrotising soft tissue infection

NSTIs are rapidly progressive infections which can be highly aggressive in destroying skin, fascia and surrounding tissue. Organisms infiltrate and migrate along the superficial and deep fascial planes, causing vascular occlusion, ischaemia and tissue necrosis. This can lead to systemic sepsis and multiple organ dysfunction (Devaney et al 2015).

There is no clear definition of NSTIs, nor is there a system of classification. They are a collection of heterogeneous conditions, the outcome of which is, in many instances, significantly influenced by early diagnosis. The term necrotising fasciitis is broadly synonymous with NSTI. Fournier's gangrene is a necrotising fasciitis of the perineum; it most commonly occurs in elderly men and in people affected by diabetes, excessive alcohol consumption or immune-compromise (Li et al 2015).

The symptoms of necrotising fasciitis develop quickly over hours or days. They may not be obvious at first and can be similar to less serious conditions such as flu, gastroenteritis or cellulitis. Early symptoms can include:

- a small but painful cut or scratch on the skin
- intense pain that is out of proportion to any damage to the skin
- a high temperature (fever) and other flu-like symptoms

After a few hours to days, the following may occur:

- swelling and redness in the painful area
- diarrhoea and vomiting
- dark blotches on the skin that turn into fluid-filled blisters

If left untreated, the infection can spread through the body quickly and cause symptoms such as dizziness, weakness and confusion (NHS Choices, 2016).

Current treatment

The standard treatment for NSTIs is surgical debridement, intensive medical support and antibiotics (Hakkarainen et al 2014).

Proposed Intervention

HBOT has been suggested as an adjunct in the treatment of NSTIs. HBOT involves the inhalation of pure oxygen at a pressure higher than normal atmospheric pressure, usually 2 to 3 atmospheres absolute (ATA). During HBOT the patient is in a pressure chamber, usually for 45 to 120 minutes at least once daily.

Inhaling oxygen at increased pressure is intended to improve oxygen supply to the infected tissue. Nearly all the oxygen in the blood is bound to haemoglobin; under normal pressure, saturation of haemoglobin in the arterial blood is around 97%. The remaining oxygen is dissolved in the blood plasma; this proportion can be increased by higher ambient pressure and the associated increase in the partial pressure of oxygen. In this way, tissue that would be rendered hypoxic by the disease process may receive a more adequate supply of oxygen, and this in turn may improve cell function, the immune response and wound healing. This might occur because of enhanced neutrophil killing ability, angiogenesis, fibroblast activity and/or collagen synthesis (Li et al 2015).

If HBOT is effective, the infection would spread more slowly and the patient would require fewer or less extensive debridements and/or less support with ventilation, inotropes and vasopressors.

HBOT carries potential hazards, including respiratory distress, pneumothorax and barotrauma.

No guidance was found from the National Institute for Health and Care Excellence on the use of HBOT in NSTIs.

2 Definitions

- **Ambient:** relating to the immediate surroundings of something.
- **Angiogenesis:** the production of new blood vessels.
- **Atmospheres absolute (ATA):** a measurement used to describe atmospheric pressure; one ATA is about roughly equivalent to sea level atmospheric pressure.
- **Barotrauma:** damage to the ear or other areas of the body because of increased pressure.

- **Cellulitis:** inflammation of subcutaneous connective tissue.
- **Collagen synthesis:** production of the supporting framework for tissues and organs.
- **Debridement:** see surgical debridement.
- **Haemoglobin:** the protein in red blood cells that carries oxygen.
- **Hypoxic:** deficiency in the amount of oxygen reaching the tissues.
- **Ischaemia:** reduction in blood flow.
- **Fascial planes:** the areas between muscle groups.
- **Fibroblast activity:** the principal active cells of connective tissue. Following tissue injury, fibroblasts migrate to the site of damage, where they deposit new collagen and facilitate the healing process.
- **Fournier's gangrene:** a type of necrotizing fasciitis affecting the perineum (the area between the pubic bone at the front and the coccyx or tail bone).
- **Heterogeneous:** diverse in character or content.
- **Immunocompromised:** a patient who does not have the ability to respond normally to an infection due to an impaired or weakened immune system.
- **Inotropes:** drugs that support blood pressure in people who are critically ill.
- **Multivariate adjustment:** controlling for confounding factors in research.
- **(Multivariate) relative risk:** risk of those exposed to an outcome(s) vs. those who not exposed
- **Neutrophil:** one of the groups of white blood cells.
- **Perineum:** the area between the pubic bone at the front and the coccyx or tail bone).
- **PICO:** a framework for defining a clinical question that aids in finding clinically relevant evidence in the literature. PICO stands for Patient/Population/Problem, Intervention, Comparison and Outcome.
- **Pneumothorax:** collapse of a lung because of air entry into the chest.
- **Randomisation:** assigning people in a research study to different groups without taking any similarities or differences between them into account. It means that each individual (or each group in the case of cluster randomisation) has the same chance of having each intervention.
- **Surgical debridement:** surgical removal of dead tissue.

- **Systemic sepsis:** infection that is widespread throughout the body and present in the blood.
- **Tissue necrosis:** the death of body tissue.
- **Vascular occlusion:** blockage of a blood vessel.
- **Vasopressors:** a group of medicines that contract (tighten) blood vessels and raise blood pressure.

3 Aims and Objectives

This policy considered the evidence underpinning the addition of HBOT to standard care for necrotising soft tissue infection.

The objectives were to:

Consider whether in the management of necrotising soft tissue infection:

- the evidence base supports HBOT as an adjuvant treatment
- the evidence base supports the place of HBOT in the care pathway
- there are any subgroups who derive additional benefit compared to others.
- there is evidence that HBOT is cost effective.

4 Epidemiology and Needs Assessment

NSTIs are rare. The actual incidence in the United Kingdom is estimated at 500 new cases each year but it is difficult to record. There are no ongoing surveillance programmes that capture data on NSTI cases caused by all organisms (Public Health England, 2016). In addition, there is uncertainty that arises from the numerous terms given to describe the same condition (Hasham et al, 2005).

NSTIs carry a risk of mortality of about 30%. They also cause long-term disability from limb and tissue loss (Hakkarainen et al 2014).

5 Evidence Base

NHS England has concluded that there is not sufficient evidence to support the routine commissioning of this treatment for the indication.

Summary of Evidence

NHS England commissioned a review of the published evidence on HBOT use for treating necrotising soft tissue infections. To aid in the search for clinically relevant literature, experts in the field of HBOT guided the development of a Population, Intervention, Comparison, Outcome (PICO) framework. Key findings were:

- Two uncontrolled studies and eight controlled but unrandomised studies were found. None of the controlled studies concealed treatment allocation from participants or researchers, creating a risk of bias.
- The studies were varied. In the larger studies covering many hospitals, the HBOT and control participants were treated in different hospitals with different regimes, introducing bias. No study matched participants in HBOT and controls arms.
- Participants were adults with NSTIs; two smaller studies (one uncontrolled) included only people with Fournier's gangrene (Li et al 2015 (n=28), Rosa et al 2015 (n=34)).
- HBOT regimes varied: five reported regimes consistent with the PICO (Krenk et al 2007 (n=19), Rosa et al 2015, Li et al 2015, Bosco et al 2015 (n=34) and George et al 2009 (n=78)), while the other five provided no information on the regime but were included because of their large size and their inclusion of controls (Soh et al 2012 (n=45,913), Mulla et al 2007 (n=216), Devaney et al 2015 (n=341), Psinos et al 2013 (n=56,527) and Shaw et al 2014 (n=1583)).
- Two controlled studies (Soh et al 2012 and Mulla et al 2007) attempted to adjust fully for the differences between the participants who underwent HBOT and those that did not; this is the most reliable approach. Another three studies (Devaney et al 2015, Shaw et al 2014 and George et al 2009) undertook multivariate adjustment but only of some results – mortality in all three studies and complications in the case of Shaw et al 2014. They also used fewer variables in the adjustment than the first two studies and so are not as sound. The other controlled studies and the unadjusted results from these three studies are at much higher risk of confounding; we do not consider them reliable.
- The trials all compared HBOT plus standard care with standard care only.

- Nine studies reported mortality. Three of the five more reliable studies reported lower mortality with HBOT (Soh et al 2012 adjusted odds ratio (OR) 0.45, 95% confidence interval (CI) 0.29 to 0.83, $p = 0.008$; Shaw et al 2014 control participants' multivariate OR 10.6, 95% CI 5.2 to 25.1, (i.e. control participants at higher risk of death); Devaney et al 2015 HBOT 33/275 (12%), control 16/66 (24%), $p = 0.01$). Two reported mortality rates with and without HBOT that were not significantly different (Mulla et al 2007 multivariate relative risk (RR) 0.48, 95% CI 0.09 to 2.56, $p = 0.39$; George et al 2009 OR 0.98, 95% CI 0.18 to 5.42).
- Li et al 2015 reported mean curative time, but did not define this outcome measure. In an unadjusted analysis, it was shorter with HBOT (HBOT 15.4 days, control 25.5 days, $p < 0.05$).
- Four studies reported, without adjustment, the mean number of debridements, of which three reported more debridements with HBOT (Devaney et al 2015 HBOT 4.8, control 3, $p < 0.001$; Krenk et al 2007 HBOT 3.36, control 0.5, $p < 0.002$; George et al 2009 HBOT 3.3, control 2.4, $p = 0.03$). The discrepant result is from Li et al 2015, reporting fewer debridements with HBOT (HBOT 1.32, control 2.17, $p < 0.05$).
- Krenk et al 2007 reported, without adjustment, no significant difference in the mean number of incision and drainage procedures with HBOT (HBOT 4.63, control 2.13, $p > 0.05$).
- Devaney et al 2015 reported, without adjustment, no significant difference in the mean number of amputations with and without HBOT (HBOT 21/275 (7.6%), control 10/66 (15.2%), $p = 0.095$ calculated by SPH).
- The same authors reported without adjustment more intensive care admissions in those treated with HBOT (HBOT 210/275 (76%), control 37/66 (64%), $p = 0.05$). George et al 2009 reported similar durations of intensive care with and without HBOT (HBOT 5.7 days, control 4.7 days, $p = 0.95$).
- George et al 2009 also reported similar mean durations of antibiotic use with and without HBOT (HBOT 18 days, control 20 days, $p = 0.97$).
- Shaw et al 2014 reported a multivariate analysis indicating there were fewer complications with HBOT (HBOT 45%, control 66%, $p < 0.01$).

- Six studies reported length of stay. Of the more reliable adjusted analyses, Soh et al 2012 reported that this was longer with HBOT (HBOT 14.3 days, 95% CI 13 to 16; control 10.7 days, 95% CI 10 to 11; $p < 0.001$), while Mulla et al 2007 reported no association between treatment and length of stay (regression coefficient¹ 0.112, 95% CI -0.332 to 0.556, $p = 0.62$).
- No studies were found reporting adverse effects of treatment.
- No studies were found on the cost effectiveness of HBOT.

Conclusion

The lack of high quality evidence and discrepancies between studies limit what can be concluded from this research. However, the more reliable studies that were found indicate, but by no means prove, that HBOT may:

- reduce mortality
- increase lengths of stay
- increase costs in people with NSTIs (these needs to be interpreted with caution as the increased costs may be associated with increased initial survival).

HBOT may also prevent complications, though there is less evidence of this.

Confidence in the studies' results is limited by the uncorrected influence of other factors not used in multivariate adjustment, such as differences in the quality and or content of care of participants who did and did not receive HBOT.

Overall, no analysis was found on whether the extra costs of HBOT are justified by any health benefits it produces. Further research would be needed to reduce the current uncertainty.

6 Documents which have informed this Policy

This document updates and replaces the present clinical commissioning policy as part of review of the use of HBOT for a range of indications:

NHS England Clinical Commissioning Policy 2013: Hyperbaric Oxygen Therapy

¹ A regression coefficient is a measure of the association between two variables, with a positive value indicating that as one rises, the others tends to rise also.

NHSCB/D/D11P/a (<https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/10/d11-p-a.pdf>)

7 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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