

Do surgical interventions for lymphoedema reduce the frequency of cellulitis attacks? A systematic review of the literature.

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Conflicts of interest

None declared

Abstract

Recurrent cellulitis is a frequent and challenging complication of lymphoedema. The cellulitis guidelines of the British Lymphology Society state that decongestive lymphatic therapy reduces the frequency of cellulitis attacks, but do not mention the effect of surgical interventions. This systematic review aims to assess whether surgical interventions for lymphoedema reduce the frequency of attacks of cellulitis.

We searched Embase, Medline and the Cochrane database for relevant articles from the inception of the databases to January 2015. 431 abstracts were retrieved. Two independent reviewers applied selection criteria, and 26 papers were selected for full text review. Two of these articles were unavailable in the UK from any source.

Of the 24 papers included, a variety of surgical techniques were utilized: lymphaticovenous anastomosis, superficial-to-deep lymphaticolymphatic anastomosis, lymph node transfer, Charles procedure, muscle flap transfer, Homan's procedure and subcutaneous tissue excision below skin flaps. Five studies combined techniques. One study compared the intervention to a control group (physical therapy). The incidence of cellulitis was decreased following surgical intervention in 23/24 studies included. Eight had a quantifiable reduction in cellulitis over a set follow-up period; in 15 the pre-operative incidence was not precisely measured.

Surgery is effective at reducing the incidence of cellulitis in lymphoedema. However, there is a lack of high quality randomized controlled trials. Future research should concentrate on comparison with control groups, for example compression alone vs. compression combined with surgical intervention, in patients with lymphoedema and greater than two attacks of cellulitis per year.

1. Introduction

Lymphoedema is a chronic condition of localized fluid retention and tissue swelling, caused by a compromised lymphatic system. Lymphoedema can be broadly categorized into two subsets: primary lymphoedema, caused by a fault in lymphatic system development¹, and secondary lymphoedema, caused by damage to the lymphatic system, commonly due to treatment of cancer, infection, or trauma². Secondary lymphoedema is now thought to affect over 100,000 people in the UK³.

1.1. Surgical interventions for lymphoedema

There is currently no cure for lymphoedema. The mainstay of treatment over the last 50 years has been conservative non-surgical therapy, such as decongestive lymphatic therapy, which aims to control symptoms by minimising the build-up of fluid. There are numerous surgical interventions that have been trialled for the treatment of lymphoedema: lymphaticovenous anastomosis (LVA), vascularised lymph node transfer (VLNT), superficial-to-deep lymphaticolymphatic anastomosis (LLA), muscle flap transfer, Charles procedure, Homan's procedure, and subcutaneous tissue excision below skin flaps. These have been used with varying success, and at present no definitive surgical treatment that has been widely adopted.

Surgical treatments for lymphedema can be broadly divided into two categories: physiological and reductive. The physiological approach attempts to reconstruct the lymphatic drainage, whereas the reductive approach focuses primarily on the excision of lymphoedematous tissue. The reductive approach was used initially:

Charles procedure

This was a technique first described by Charles in 1912⁴ for the treatment of lower limb elephantiasis. The affected lymphoedematous skin and subcutaneous tissue is resected down to the muscle fascia, and the area is covered with skin grafts taken from the resected specimen.

Homan's procedure

This procedure was also first described for the treatment of elephantiasis, by the eponymous surgeon in 1936⁵. The procedure consists of a tissue resection below preserved skin flaps, with the skin flaps used to cover the resected area, to achieve a more aesthetically pleasing result.

Muscle flaps

The buried dermis flap technique was devised by Thompson and described in 1962⁶. It consists of raising thinned skin flaps throughout the length of the lymphoedematous limb, excising underlying subcutaneous fat and deep fascia, and then closing the wound by burying the posterior skin flap into the deep muscles (along the line of the main vessels) after denuding it of all epidermis. In addition to directly reducing limb circumference, this has also been postulated to improve drainage of lymph fluid.

Suction-assisted protein lipectomy (SAPL)

SAPL was later developed as a minimally invasive procedure that addresses the fatty component of lymphedema, which typically occurs later in the disease process and presents as chronic non-pitting lymphedema⁷.

More recently, technological advances have brought microsurgery to the forefront of this field. Microsurgical reconstructive work with lymphatics to treat lymphedema began in the 1960s, and has since been refined and improved, leading to the

development of the supermicrosurgical techniques of LVA⁷⁻¹⁴ and LLA¹⁵. These developments have presented a less invasive surgical option for patients with lymphoedema, as well as a better aesthetic outcome than reductive surgery.

LVA

LVA is used to divert lymphatic fluid into the venous system before it reaches an area of lymphatic compromise by anastomosing lymphatics to veins distal to the obstruction, thus providing a physiological bypass. A large recent case series looking at the outcome of LVA showed 83% of patients experienced a mean reduction of 76% of the excess volume¹⁴.

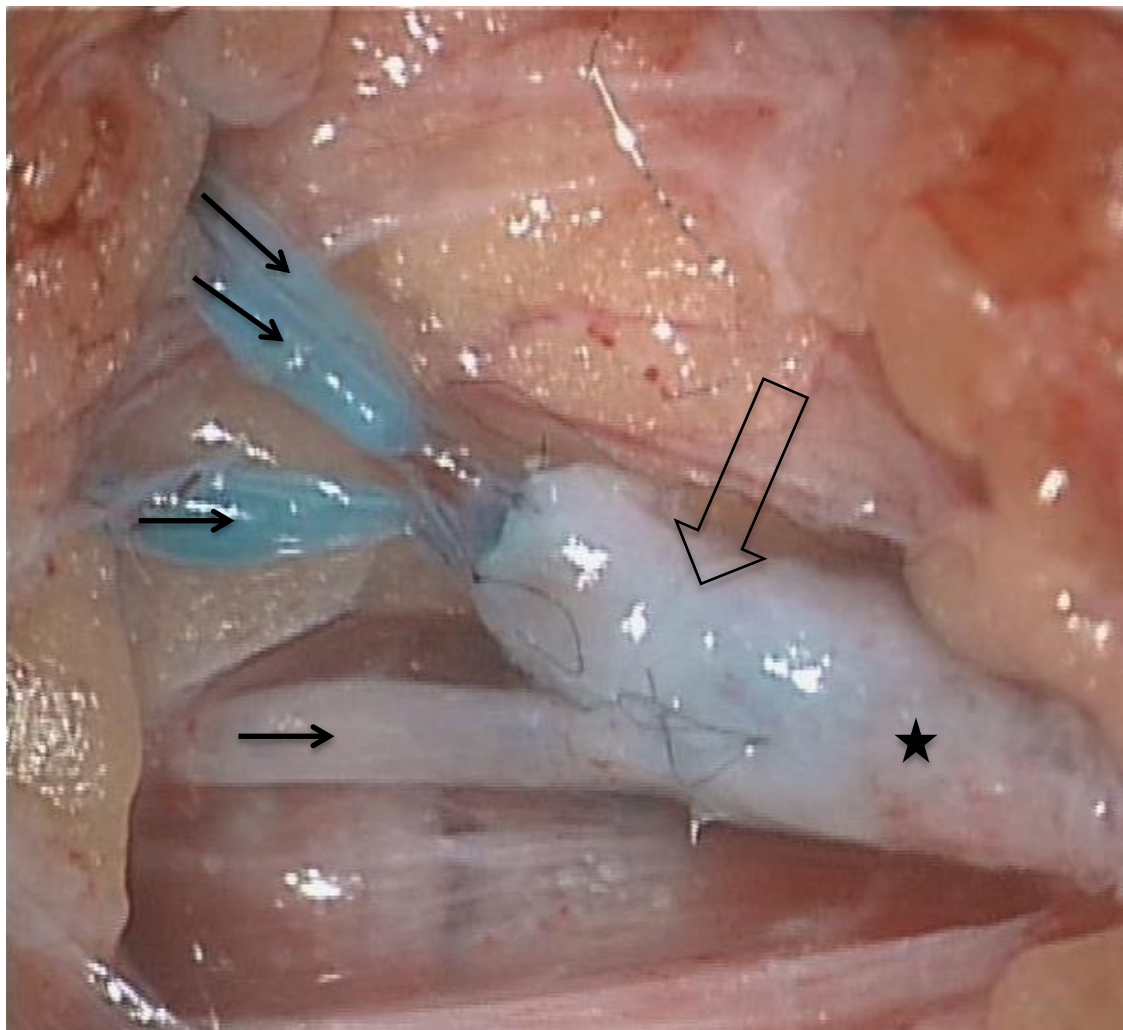


Figure 1. A lymphaticovenular anastomosis. Several small lymphatics, some of which are marked by patent blue staining of the lymphatic fluid (filled arrows), have been anastomosed to a single vein (asterisk). Flow of lymphatic fluid into the venous system is demonstrated by blue staining inside the vein (unfilled arrow).

LLA

Baumeister¹⁶ was one of the first to describe LLA. This paper detailed a case series of 55 patients with volume reduction of a lymphoedematous limb, after a lymphatic graft was used to anastomose intact proximal groin lymphatics with the lymphatics of a contralateral unaffected thigh. LLA is thought to have a lower risk of anastomotic site

thrombosis¹⁵ than LVA, but has limited indications due to the requirement of a local intact deep lymphatic system.

VLNT

This technique was first described by Becker et al¹⁷ over twenty years ago. VLNT involves the transfer of healthy vascularized lymph nodes within a block of tissue from a donor site to the lymphoedematous limb. The mechanism of action is unknown, possibly the transfer of healthy lymph nodes and lymphatics either directly drains excess lymph fluid from oedematous areas via intra-flap lymphatico-venous connections, or encourages new lymphatic vessels to sprout in the region¹⁸. The majority of recent studies looking at VLNT have found a mean volume reduction of almost half of lymphoedematous volume¹⁹, although one disadvantage of this technique is the possibility of lymphedema occurrence in the donor site⁷.

A review of contemporary literature on surgical treatment for lymphedema assessed the effect of these treatments options on volume reduction¹⁹. This found that the mean volume reduction was greatest for reductive techniques (SAPL being the technique used in the majority of cases). However, this is to be expected as this involves the physical removal of the space-occupying solid component of lymphoedematous tissues. While physiological techniques result in less volume reduction, they have fewer requirements for compression post-operatively as they reconstruct lymphatic function. Indeed, in the largest series (n=1800) of LVA with the longest follow-up (10 years), 85% of patients discontinued their use of conservative treatment¹⁴. Conversely, stringent post-operative compression is key to the success of SAPL and other excisional treatments.

1.2 Cellulitis

Cellulitis is defined as an acute inflammation of the skin and subcutaneous tissue and is commonly caused by *Streptococcus pyogenes* or *Staphylococcus aureus*²⁰. It is strongly associated with lymphedema²¹. Moffett et al³, showed that 28% of patients with lymphoedema had had an episode of cellulitis within the previous 12 months. Similarly, Dupuy²² found that lymphoedema was present the strongest risk factor for development of cellulitis of the leg. These findings have been verified using lymphoscintigraphy in patients with two or more previous episodes of cellulitis²³. This confirmed that recurrent cellulitis might be underpinned by lymphatic abnormalities. Interestingly, 60% of these patients also had abnormal lymphoscintigrams in their unaffected leg, suggesting pre-existing lymphatic abnormalities can precede the occurrence of clinical cellulitis.

As such, cellulitis remains a common and disabling complication of lymphoedema. Whilst decongestive lymphatic therapy has been shown to reduce the frequency of cellulitis attacks, there is little systematic evidence as to whether surgical interventions reduce the incidence of cellulitis. This review examines the effects of these interventions on the incidence of cellulitis in patients with lymphoedema.

2. Methods

We searched Medline, Embase and the Cochrane database from inception to January 2015, restricted to papers published in English, using the following strategy:

1. Lymphedema/ OR lymphatic obstruction.ti,ab. OR lymphoedema.ti,ab. OR lymphedema.ti,ab. OR milroys.ti,ab. *AND*
2. Cellulitis/ OR cellulitis.ti,ab. OR inflammatory erysipelas.ti,ab. *AND*
3. Exp Specialties, Surgical/ OR surg*.ti,ab. OR operat*.ti,ab. OR lva.ti,ab. OR lymphaticovenous anastomosis.ti,ab. OR suction assisted protein lipectomy.ti,ab. OR Microsurgery/ OR microsurgery.ti,ab. OR Lipectomy/ OR lipectom*.ti,ab. OR sapl.ti,ab. OR vascularized lymph node transfer*.ti,ab. OR lymphaticolymphatic bypass.ti,ab. OR lymphatic liposuction.ti,ab.

Two review authors (AS and SK) independently determined the eligibility of each study. Both review authors analysed the titles and abstracts of all citations found through the search strategy above. Papers that did not have an abstract containing information about a surgical intervention for lymphoedema and cellulitis were excluded. A copy of the full article was obtained for each reference reporting a potentially eligible trial, and the two review authors independently applied the eligibility criteria: papers which did not contain quantitative data on the incidence of cellulitis pre- and post-surgical intervention and those whose data was duplicated in another paper were excluded; discrepancies were resolved by consensus discussion with a third review author (DF). Full details of all eligible studies were obtained. The search strategy was limited to studies reported in English.

3. Results

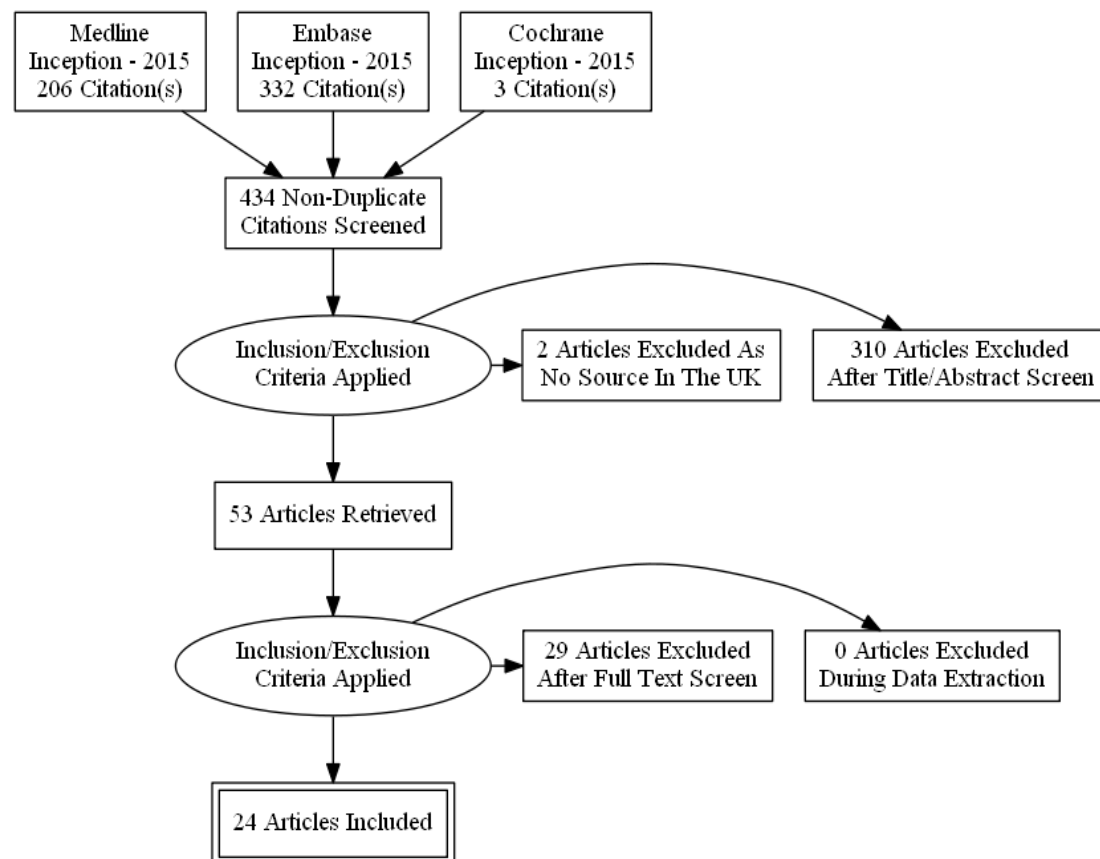


Figure 2. Study flow diagram

Two studies^{24,25} were excluded because there was no copy of the paper available from any source in the UK.

Of the 24 papers included, a variety of surgical techniques were utilized: lymphaticovenous anastomosis⁸⁻¹⁴, lymph node transfer²⁶⁻²⁸, superficial-to-deep lymphaticolymphatic anastomosis¹⁵, muscle flap transfer or buried muscle flap²⁹⁻³², Charles procedure^{33,34}, Homan's procedure³⁵, and subcutaneous tissue excision below skin flaps³⁶. Five studies combined techniques. The first of these used SAPL followed by VNLT³⁷; the second a hybrid technique incorporating the Charles procedure and VLNT³⁸; the third a hybrid technique combining VLNT and LVA³⁹; and the fourth primarily used LVA, with some patients also undergoing segmental reduction secondarily⁹. The fifth study³² used a musculocutaneous flap in four patients; one of these also underwent LVA in the same procedure. Only one study²⁸ compared the intervention to a control group (physical therapy).

The incidence of cellulitis was decreased following surgical intervention in 23/24 studies included. The only paper that failed to show a decrease in cellulitis incidence used the buried dermis flap and was published in 1974²⁹. However, a later paper³⁰, published in 1980, did show a reduced incidence of cellulitis using the same technique. Eight had a quantifiable reduction in cellulitis over a set follow-up period; in 15 the pre-operative incidence was not precisely measured. Results stratified by technique are described below.

3.1 Reductive Approach

Three papers looked at the use of reductive flaps in lymphoedema treatment; two were buried dermis flaps while the third used subcutaneous excision beneath skin flaps. Two of these showed a reduced incidence of cellulitis post-operatively, while the third showed no change. Two papers looked at the Charles procedure. Both showed a reduction in the incidence of cellulitis post-operatively. One paper used Homan's procedure. Of the 39 patients, 11 had cellulitis attacks pre-operatively, while none had any in the follow-up period. Two papers used SAPL. Both showed a reduction in the incidence of cellulitis post-operatively. In the following tables, the Granzow⁷ paper includes patients treated with LVA, VNLT and SAPL. The outcomes of these techniques have been separated to allow comparison with other studies.

	Technique		n	Average follow up (months)	Pre-operative incidence of cellulitis	Post-operative incidence of cellulitis
Sawhney 1974 ²⁹	Flaps	Buried dermis flap	5	'Up to 24'	Recurrent	Recurrent (no change)
Miller 1975 ³⁶		Subcutaneous excision beneath skin flaps	14	6-72	9 patients had >2 previous episodes	0
Thompson 1980 ³⁰		Buried dermis flap	140	96	39%	30%-significantly reduced in 23%, no change in 7%
Bauer 2002 ³³	Charles Procedure		1	12	Recurrent	0
Karri 2011 ³⁴			27	21.6	Recurrent in 70%	Single episode in 18.5%
Feins 1977 ³⁵	Homan's Procedure		39	'Up to 60'	'Attacks present in 11 patients pre-op'	0
Brorson 1997 ⁴⁰	SAPL		12	12	0.4	0.1
Granzow 2014 ⁷			10	12	70%	10%

3.2 Physiological Approach

There were eight papers that looked at cellulitis outcomes in LVA. All showed a marked decrease in the incidence of cellulitis after LVA. Four studies reported the incidence of cellulitis after VLNT. The incidence of cellulitis was reduced post-operatively in all four papers. One paper used LLA in a case study of one patient. Cellulitis was eliminated during the follow-up period in this patient. Two studies

	Technique	n	Average follow up (m)	Pre-operative incidence of cellulitis	Post-operative incidence of cellulitis
Gloviczki 1988 ⁸	LVA	14	36.6	5 had 'recurrent' pre-op	1/5 has 'recurrent' post-op. 1 other with no cellulitis pre-op developed cellulitis post-op
O'Brien 1990 ⁹		90 (38/90 had LVA plus additional reductive surgery)	50.4	LVA alone: 21% of LVA plus reductive surgery: 39%	LVA alone: 11% LVA plus reductive surgery: 13%
Matsubara 2006 ¹⁰		9	68	2.4/ year	0.2
Mihara 2012		1	8	10 episodes in 5 years	0
Mihara 2012		1	30	4 episodes over 2 years	0
Mihara 2014 ³⁹		95	27.3	1.46/ year	0.18/ year
Campisi 2010 ¹⁴		'>1800'; a proportion followed up but number not stated	>120	Not stated	87% reduction
Granzow 2014 ⁷		8	27	58%	15%

Lin 2009 ²⁶	VLNT		13	56.3+/- 27.12	Not stated	Incidence decreased in 11/13 patients
Cheng 2012 ²⁷			6	8.7±4.2	3.9±4.3 episodes over 71±42.2 months	0.1±0.4
Cheng 2013 ²⁸			10 patients and 10 controls (physical therapy alone)	39.1 ± 15	P: 2.2 +/- 0.8 C: 1.1 +/- 0.7	P: 0.3 +/- 0.5 C: 0.4 +/- 0.5
Granzow 2014 ³⁷			2	Patient 1 had VLNT at 11 months, Patient 2 at 22 months. Doesn't state actual follow up time	Repeated	0
Granzow 2014 ⁷			8	32	54%	19%
Yamamoto 2015 ¹⁵	LLA		1	6	>10/year	0
Classen 2005 ³¹	Flaps	Free muscle flap transfer	1	36	3 over 2 years	0
Parrett 2009 ³²		Musculo- cutaneous flap with cutaneous pedicle (plus LVA in one)	4	31	Recurren t	0

4. Discussion

Recurrent cellulitis is a significant problem for patients with lymphoedema. Lymphoedema is a major risk factor for the development of cellulitis, while cellulitis in turn exacerbates lymphoedema. The resulting cellulitis requires not only antibiotic treatment, but often prophylactic antibiotics in an attempt to reduce the rate of recurrence. However, treatment of the infection does not relieve the underlying cause, and prophylaxis is not always successful. In these patients, new therapeutic approaches are urgently required.

The British Lymphology Society guidelines provide evidence for the use of decongestive therapy to treat lymphoedema as a method of cellulitis treatment, however they contain no guidance on the use of surgical management. The results of this review show surgical interventions are consistently effective in decreasing the incidence of cellulitis, despite limitations in study design and reporting.

The plethora of surgical interventions for lymphoedema is indicative of the current lack of knowledge as to the most effective technique. All of the techniques reviewed here reduce the post-operative incidence of cellulitis, and each offers their own advantages and disadvantages. Physiological techniques tend to have more moderate effects on volume reduction, while reductive techniques require a great deal of post-operative care. As such, the optimal treatment of these patients is decided on a case-by-case basis. Given this, when considering the most appropriate therapy for a patient with lymphoedema and recurrent cellulitis, the risk of surgical complications and the aesthetic result of the surgery are likely to be important factors in decision-making. LVA has the largest body of evidence suggesting a reduction in the post-operative incidence of cellulitis, and is also the least invasive technique. This would therefore seem to be the most logical first surgical intervention.

However, it remains difficult to suggest there is a definitive 'best' technique, given the relatively low level evidence presented in the papers suitable for this review. According to the Centre for Evidence-Based Medicine (CEBM)⁴¹, none of the papers included would have scored higher than a '3b'. This poor level of evidence is often as a result of restrictions in the paper's methodology, caused by low follow-up rates, inadequate data recording and small numbers of patients. As previously mentioned, only one paper²⁸ included a control group. In this paper, the control group received physical therapy rather than a surgical intervention, and also showed a decrease in the incidence of cellulitis. This confounds the results, as the majority of studies included in this review use surgery combined with some form of conservative therapy both pre and post operatively. It is therefore difficult to understand what proportion of the reduction in the incidence of cellulitis is directly due to the surgical intervention. In addition, the use of hybrid techniques also makes analysis of results more difficult, and again makes it more difficult to recommend a single 'best' technique. Currently, there are no comparative randomized-controlled trials that compare surgical treatments with the current standard therapy alone in terms of cellulitis outcome. We believe there is an urgent need for such trials in order to determine the optimal treatment of this challenging group of patients.

5. Conclusion

Several different types of surgical techniques have been applied to the improvement of lymphoedema and its related complications. This systematic review of the literature shows that they are almost globally successful in the post-operative reduction of cellulitis incidence, and suggests surgery to be promising for the management of cellulitis secondary to lymphoedema. However, most of the evidence is of poor quality (CEBM level 3b or lower), suffering from small numbers of participants, who are followed up for periods that are too short for a chronic condition. Measurement of the incidence of cellulitis is inconsistent and often non-quantitative. To draw more reliable conclusions a high quality randomised controlled trial (RCT) is required. As LVA was the method most commonly used, is the most minimally invasive, and has the largest evidence base, we propose the urgent need for a RCT of LVA plus compression versus compression alone for a group of patients with more than two episodes of cellulitis per year despite optimal medical therapy.

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