ORIGINAL ARTICLE

Compression Therapy to Prevent Recurrent Cellulitis of the Leg

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ABSTRACT

BACKGROUND

Chronic edema of the leg is a risk factor for cellulitis. Daily use of compression garments on the leg has been recommended to prevent the recurrence of cellulitis, but there is limited evidence from trials regarding its effectiveness.

METHODS

In this single-center, randomized, nonblinded trial, we assigned participants with chronic edema of the leg and recurrent cellulitis, in a 1:1 ratio, to receive leg compression therapy plus education on cellulitis prevention (compression group) or education alone (control group). Follow-up occurred every 6 months for up to 3 years or until 45 episodes of cellulitis had occurred in the trial. The primary outcome was the recurrence of cellulitis. Participants in the control group who had an episode of cellulitis crossed over to the compression group. Secondary outcomes included cellulitis-related hospital admission and quality-of-life assessments.

RESULTS

A total of 183 patients were screened, and 84 were enrolled; 41 participants were assigned to the compression group, and 43 to the control group. At the time of a planned interim analysis, when 23 episodes of cellulitis had occurred, 6 participants (15%) in the compression group and 17 (40%) in the control group had had an episode of cellulitis (hazard ratio, 0.23; 95% confidence interval [CI], 0.09 to 0.59; P=0.002; relative risk [post hoc analysis], 0.37; 95% CI, 0.16 to 0.84; P=0.02), and the trial was stopped for efficacy. A total of 3 participants (7%) in the compression group and 6 (14%) in the control group were hospitalized for cellulitis (hazard ratio, 0.38; 95% CI, 0.09 to 1.59). Most quality-of-life outcomes did not differ between the two groups. No adverse events occurred during the trial.

CONCLUSIONS

In this small, single-center, nonblinded trial involving patients with chronic edema of the leg and cellulitis, compression therapy resulted in a lower incidence of recurrence of cellulitis than conservative treatment. (Funded by Calvary Public Hospital Bruce; Australian and New Zealand Clinical Trials Registry number, ACTRN12617000412336.)

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N Engl J Med 2020;383:630-9.
DOI: 10.1056/NEJMoa1917197

Cellulitis is a common bacterial infection of the skin and subcutaneous tissue that occurs mostly in the legs and is associated with health care costs[1] and adverse health outcomes.[2] Recurrence of cellulitis is common: up to 47% of patients have a recurrent episode within 3 years.[3] Penicillin prophylaxis is effective in preventing recurrence of cellulitis, although a trial published in the *Journal* in 2013 showed that the protective effect diminishes progressively once the antibiotic agent is discontinued.[4] A Cochrane review of interventions to prevent cellulitis identified six studies investigating prophylactic antibiotics, but no randomized trials of other interventions such as edema management were identified.[5] The efficacy of nonantibiotic treatments to prevent cellulitis has not been well studied.[5,6]

Chronic edema refers to swelling that persists for 3 months or longer and has various and often mixed causes. The principal cause of edema may be increased capillary filtration or failure of lymphatic drainage,[7,8] which results from conditions such as lymphedema, venous hypertension, immobility, obesity, and heart failure. Chronic edema is a risk factor for cellulitis of the leg and for recurrent cellulitis.[3,9-11]

Compression therapy has been used to reduce and control chronic edema. This treatment involves the daily wearing of compression garments such as stockings, with or without a short period of compression bandaging to reduce swelling before compression garments are fitted. Compression garments and bandages exert the greatest degree of compression at the ankle and gradually apply less pressure proximally along the limb. By exerting this type of graduated pressure on the leg, compression therapy reduces the formation and accumulation of interstitial fluid and shifts fluid proximally, away from the lower leg.[12] Guidelines have suggested the use of compression therapy to prevent recurrent cellulitis in patients with chronic edema of the leg, and compression therapy is widely used by clinicians[2,3,13,14]; however, there are limited data from trials to support this practice. We conducted a randomized, controlled, single-center trial to determine whether compression therapy would prevent the recurrence of cellulitis of the leg in adults with chronic edema of the leg.

METHODS

TRIAL DESIGN AND OVERSIGHT

Participants were randomly assigned in a 1:1 ratio to receive either compression therapy plus education regarding prevention of cellulitis (compression group) or education alone (control group). Randomization was stratified according to prophylactic antibiotic use (yes or no), with a planned maximum follow-up of 3 years. Participants in the control group crossed over to the compression group when they had an episode of cellulitis. Assessors and participants were aware of the trial-group assignments.

The trial was conducted at Calvary Public Hospital Bruce (Canberra, Australia). The protocol (available with the full text of this article at NEJM.org) was approved by three institutional human research ethics committees. Participants provided written informed consent before the trial. The authors designed and implemented the trial and collected and analyzed the data. The first author wrote the first draft of the manuscript, and all authors contributed to subsequent drafts. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. Haddenham Healthcare manufactured and provided the compression garments but had no involvement in the design, conduct, analysis, or reporting of the trial and did not have access to the trial data.

PARTICIPANTS

Participants were recruited at one of two primary public hospitals or were referred by general practitioners servicing the local region. Patients were eligible to participate if they had a history of two or more episodes of cellulitis in the same leg in the 2 years before referral to the trial and had edema lasting longer than 3 months in one or both legs, with recurrent cellulitis. Full inclusion and exclusion criteria are provided in the protocol. The presence of edema was confirmed by means of interview and physical examination by specialist lymphedema physiotherapists. Patients were excluded from the trial if they were younger than 18 years of age, were already wearing effective compression garments 5 or more days per week, were receiving end-of-life care, had a clinically unstable condition, or had a chronic

wound or a wound requiring specialist treatment, or if compression therapy was contraindicated.

Compression garments are categorized by manufacturers into four numbered classes according to the pressure they exert at the ankle.[15] If patients were already wearing garments of compression class 2 or higher (providing 23 to 32 mm Hg of pressure), the garments were considered to be effective and the patients were excluded from the trial. Patients who were wearing class 1 garments (providing 18 to 21 mm Hg of pressure) were excluded if a lymphedema therapist determined that this lower amount of pressure was effective for the patient.

INTERVENTIONS AND ASSESSMENTS

All assessments and interventions were performed in the outpatient department of the hospital by specialist lymphedema physiotherapists who were aware of the trial-group assignments. Baseline measures, including demographic characteristics, leg volume, and quality of life, were recorded before randomization. Cellulitis was diagnosed by general medical practitioners or by hospital physicians who were not otherwise involved in the trial; the diagnosis was confirmed by trial assessors. Trial assessors verified the dates of recurrence and hospitalization with the use of medical records. Participants were encouraged to report episodes of cellulitis at the time that they occurred. In addition, participants were interviewed at the 6-month follow-up appointments to determine whether there had been unreported recurrences of cellulitis. If a recurrence was reported between scheduled follow-up appointments, participants were seen for an additional appointment with a lymphedema therapist to record outcome measures (date of cellulitis diagnosis and associated hospitalization); participants in the control group commenced crossover to the compression group at this time. An episode of cellulitis was recorded only if it occurred in a leg in which chronic edema had been identified at baseline; in the case of edema in both legs, recurrence of cellulitis was recorded as a single event if it occurred in either leg. Quality-of-life measures, leg volume, adherence to wearing garments in the compression group, and adverse events were assessed at the 6-month appointments. If participants could not attend their scheduled appointments, assessment was performed by means of telephone to check for cellulitis recurrence and associated hospital admission; quality-of-life assessments were obtained by means of mailed surveys.

Education about cellulitis prevention was provided to participants in the two trial groups at the initial appointment and at follow-up appointments and included information on the benefits of skin care, prevention of interdigital fungal infections, healthy body weight, and regular exercise. Participants assigned to the compression group were instructed to wear compression garments throughout the day and were provided information on use, safety, cleanliness, and application and removal of the garments. Two free sets of compression garments were provided to participants in the compression group at the beginning of the trial and to participants in the control group when they crossed over to the compression group.

When appropriate, a short period (typically 3 to 5 days) of therapist-applied compression bandaging to minimize edema was provided immediately before the compression garments were fitted (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The majority of prescribed compression garments were knee-high compression stockings that included the foot, with or without the toes (Fig. S2); less often, leg-and-foot compression wraps were prescribed (Fig. S3). The number of appointments required to provide compression therapy was not prespecified and varied according to the individual needs of the participants.

The prescribed garment type and compression class were determined on the basis of edema severity, leg shape, skin condition, and the ease of application and removal by the participants or their caregivers. If chronic edema was present in both legs, compression therapy was provided for both legs. Replacement of compression garments was recommended after 6 to 12 months of wear, with no restrictions on the brand used.

Participants in the control group who had an episode of cellulitis crossed over to the compression group to receive compression therapy. The date of crossover was defined as the day that compression garments were initially fitted. Participation in the trial was terminated in the case of death, withdrawal of consent, or development of a wound or lymphorrhea for which management with compression therapy was advised and was supported by evidence.[16] No further outcome

measures were obtained for participants who were withdrawn from the trial.

OUTCOMES

The primary outcome was the recurrence of cellulitis. Secondary outcomes were cellulitis-related hospital admission, change in leg volume, and quality-of-life measures. Leg volume was measured with the use of a perometer (an optoelectronic imaging device). Scanning was performed on the leg starting at a height of 5.3 cm from the bottom of the foot and extending up the leg to a height of 40.0 cm (Fig. S4). The perometer was calibrated to a standardized object every 2 weeks throughout the trial to ensure reliability.

Quality of life was assessed with the use of the quality-of-life measure for limb lymphedema (LYMQOL)[17] and the EuroQol Group 5–Dimensions 3-Level scale (EQ-5D-3L).[18] The LYMQOL consists of two components that are assessed separately: a quality-of-life score (scores range from 0 to 10, with higher scores indicating better quality of life) and a combined score that encompasses four domains (symptoms, appearance, function, and mood), each scored at four levels (not at all, a little, quite a bit, or a lot; combined scores range from 4 to 16, with lower scores indicating better quality of life).[17] The EQ-5D-3L also consists of two components that are assessed separately: a visual analogue scale that assesses the overall health state (scores range from 0 [worst imaginable health state] to 100 [best imaginable health state]) and a descriptive system that assesses five dimensions of quality of life (mobility, personal care, usual activities, pain and discomfort, and anxiety and depression) at three levels (no problems, some problems, or extreme problems; total scores for the descriptive system range from 5 to 15, with lower scores indicating better quality of life).[18]

Adherence to the intervention in the compression group was determined on the basis of the number of days per week that garments were worn. Adverse effects were reported by participants during the 6-month assessments with therapists.

STATISTICAL ANALYSIS

Assuming that recurrence of cellulitis at 3 years would occur in 47% of participants in the control group (on the basis of previous reports[3,4]) and that there would be a 50% lower incidence of cellulitis in the compression group than in the control group,[19,20] we calculated that 45 events of cellulitis would be needed to give the trial 80% power to detect a hazard ratio for recurrence of cellulitis of 0.42, at a one-sided type I error rate of 2.5%. On the basis of these assumptions, we planned to recruit 162 participants (see the Supplementary Appendix). Randomization was stratified according to prophylactic antibiotic use, with the use of block sizes of 10. To prevent bias in assignment of participants to a particular group, sealed, opaque, sequentially numbered, identical envelopes were used to ensure concealment of trial-group assignments.

The statistical analysis plan prespecified that after 23 episodes of cellulitis had occurred, an independent data monitoring committee would review the results of the interim analysis and recommend whether the trial should stop early. A post hoc stopping rule for the time-to-event analysis was determined on the basis of a one-sided significance level of 0.003 with the use of a log-rank test. If the trial continued until 45 episodes of cellulitis occurred, the final analysis would use a log-rank test with a one-sided significance level of 0.0238 to preserve an overall type I error rate of 5%.

Only data collected on or before the first interim analysis were used in the intention-to-treat analysis of the primary outcome and the secondary outcome of cellulitis-related hospital admission. Therefore, no data on outcomes for participants who crossed over to the compression group were included in the primary analysis. For the secondary outcomes of leg volume and quality of life, data for each participant in the control group were collected until crossover occurred, and data for participants in the compression group were collected until the last participant in the control group crossed over to the compression group.

Kaplan–Meier plots were used for the analysis of the primary outcome and for the analysis of the secondary outcome of cellulitis-related hospital admission. The log-rank test was used to test for between-group differences. Cox proportional-hazards regression was used to estimate the hazard ratios and to assess the contribution of other risk factors for cellulitis. The proportional-hazards assumption was assessed with the use of correlation of scaled Schoenfeld residuals and transformed survival time (cox.zph in the survival package of R software [R Project

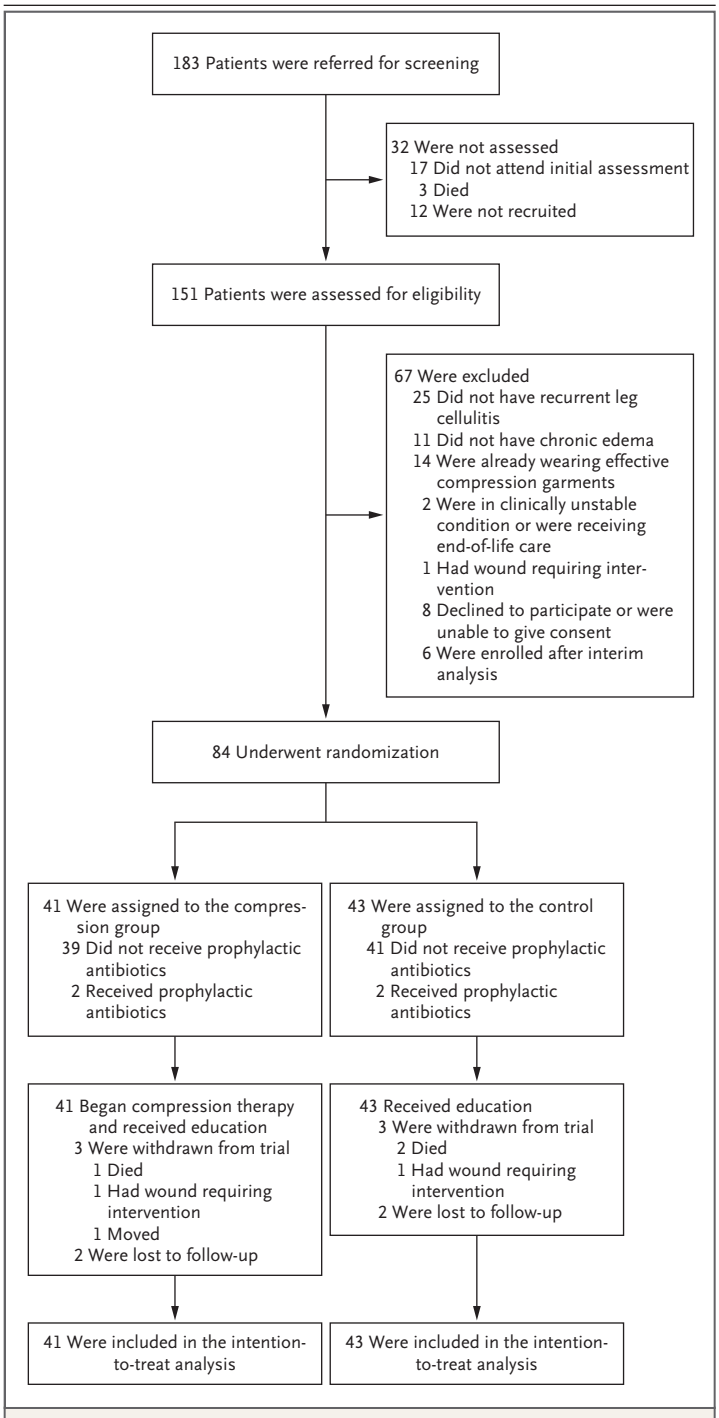

Figure 1. Eligibility, Randomization, and Follow-up.

for Statistical Computing]). Because the proportional-hazards assumption was not met, a post hoc analysis of relative risk was performed. Data for participants who were lost to follow-up were censored at the time of the last contact.

Mixed-effects linear models were used to assess between-group differences in the change in leg volume and quality of life over time, with group and time as fixed effects and participant identification number as the random effect. The two components of each quality-of-life scale were analyzed separately. Missing data were assumed to be missing at random. There was no plan for adjustment for multiple comparisons in the analyses of secondary outcomes, and the widths of confidence intervals were not adjusted for multiplicity; therefore, no clinical conclusions can be made from these data. The statistical analysis plan is available with the protocol. All analyses were performed with the use of R software, version 3.6.0.[21]

RESULTS

PARTICIPANTS

A total of 183 patients were screened and 84 were enrolled from June 2017 through February 2019 (Fig. 1). In September 2018, after nine events of cellulitis had occurred in 67 participants, lymphedema therapists who were aware of the trial-group assignments noted that there may have been a large between-group difference in recurrence. This potential difference between groups was brought to the attention of the human research ethics committees overseeing the trial. Therefore, in September 2018, the committees advised the introduction of stopping rules to ensure that the trial population was not exposed to risk, and an interim analysis plan with formal stopping rules was prepared and added as an amendment to the protocol. On March 26, 2019, the data monitoring committee advised, on the basis of the post hoc stopping rule, that the trial should be stopped for efficacy and recruitment should cease; the committee also recommended that crossover should commence to provide participants in the control group with compression therapy.

At the time that the trial was stopped, 41 participants had been assigned to the compression group, and 43 to the control group. During the trial, 2 participants (5%) in each group were lost to follow-up. Data for 3 participants (7%) in the compression group were censored because of death (1 [2%]), occurrence of a wound (1 [2%]), and relocation to a different state (1 [2%]). In the control group, 3 participants (7%) were with-

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Compression (N=41)	Control (N=43)	Total (N=84)
Age			
Mean	65.0±15.1	64.0±12.9	64.0±13.9
Median (interquartile range)	68 (52–75)	66 (57–72)	66 (55–74)
Female sex — no. (%)	19 (46)	22 (51)	41 (49)
Body-mass index†			
Mean	39.0±10.0	42.0±9.8	41.0±9.9
Median (interquartile range)	39 (31–47)	41 (34–47)	40 (33–47)
Chronic edema in both legs — no. (%)	32 (78)	34 (79)	66 (79)
Duration of edema — no. (%)			
1–5 yr	14 (34)	17 (40)	31 (37)
>5 yr	27 (66)	26 (60)	53 (63)
Episodes of cellulitis per leg in the 2 yr before trial referral‡			
Mean	2.0±1.5	2.0±1.4	2.0±1.5
Median (interquartile range)	2 (0–2)	2 (1–2)	2 (0–2)
Hospital admissions for cellulitis in the 2 yr before trial referral			
Mean	1.0±0.9	1.0±1.5	1.0±1.2
Median (interquartile range)	1 (0–2)	1 (0–1.5)	1 (0–2)
Prophylactic antibiotic use — no. (%)	2 (5)	2 (5)	4 (5)
Factors contributing to chronic edema — no. (%)			
Obesity	26 (63)	27 (63)	53 (63)
Surgery or trauma	14 (34)	13 (30)	27 (32)
Venous hypertension	15 (37)	11 (26)	26 (31)
Immobility	3 (7)	7 (16)	10 (12)
Primary lymphedema	3 (7)	2 (5)	5 (6)
Cancer	0	1 (2)	1 (1)
Other	6 (15)	3 (7)	9 (11)
Coexisting conditions — no. (%)			
Tinea pedis	13 (32)	17 (40)	30 (36)
Diabetes	10 (24)	14 (33)	24 (29)
Chronic venous insufficiency	12 (29)	11 (26)	23 (27)
Congestive heart failure	10 (24)	7 (16)	17 (20)

* Plus–minus values are means ±SD. It is assumed that all participants had some degree of edema related to previous episodes of cellulitis.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Both legs were assessed for previous episodes of cellulitis.

drawn because of death (2 [5%]) and occurrence of a wound (1 [2%]) (Fig. 1).

Baseline demographic characteristics were similar in the two groups (Table 1). Two participants in each group were using prophylactic antibiotics at the time of enrollment and continued using them throughout the course of the trial. No other participants used prophylactic antibiotics before an episode of cellulitis during the trial. Before provision of compression garments, 24 participants in the compression group received therapist-applied compression bandaging

to minimize leg edema. Compression stockings were prescribed for all participants in the compression group, and a combination of compression stockings and compression wraps were prescribed for 3 participants.

At the time of the interim analysis, the follow-up time ranged from 0 to 511 days, with a median of 186 days. Participants who had not had an event of cellulitis or a follow-up appointment at the time of the interim analysis were recorded as having had 0 days of follow-up. The median follow-up was 209 days in the compression group and 77 days in the control group. The median follow-up was short in the control group because of the participants whose data were censored after they had had an episode of cellulitis. Because data collection for leg volume and quality-of-life outcomes continued for participants in the control group until they crossed over to the compression group and continued for participants in the compression group until the last participant in the control group crossed over, the median follow-up in the two groups was 336 days for those outcomes.

Before the interim analysis was performed, 88% of the participants in the compression group reported during a follow-up interview that they wore the garments 4 or more days per week, and 73% reported that they wore the garments 5 or more days per week. No adverse outcomes were reported in participants who wore compression stockings or compression wraps.

OUTCOMES

At the time the trial was stopped, recurrence of cellulitis (the primary outcome) had occurred in 6 of 41 participants (15%) in the compression group and in 17 of 43 (40%) in the control group (hazard ratio, 0.23; 95% confidence interval [CI], 0.09 to 0.59; P=0.002) (Table 2 and Fig. 2). Because the proportional-hazards assumption was not met, relative risk was calculated post hoc. The relative risk was 0.37 (95% CI, 0.16 to 0.84; P=0.02), favoring the compression group. Table S1 shows the results of the exploratory analysis of the influence of factors that are typically associated with recurrent cellulitis (body-mass index [BMI, the weight in kilograms divided by the square of the height in meters] ≥40, tinea pedis or toe-web intertrigo, ≥3 episodes of cellulitis in either leg in the 2 years before enrollment, or development of a wound during the trial).[4,10,22]

Hospital admission for cellulitis (a secondary outcome) occurred in 3 participants (7%) in the compression group and in 6 (14%) in the control group (hazard ratio, 0.38; 95% CI, 0.09 to 1.59) at the time of the interim analysis (Table 2). After 6 months, 1 participant (2%) in the compression group and 5 (12%) in the control group had been hospitalized for cellulitis (Fig. S5). After 12 months, the mean leg volume among participants in the compression group was 181 ml less than that at baseline; among participants in the control group, the mean leg volume had increased by 60 ml (between-group difference in change, −241 ml; 95% CI, −365 to −117) (Table 2 and Fig. S6).

At 12 months, the mean LYMQOL combined score had decreased (reflecting a better quality of life) by 0.5 points in the compression group and by 0.2 points in the control group (between-group difference in change, −0.3 points; 95% CI, −0.6 to −0.1) (Table 2). There were no substantial between-group differences in the LYMQOL quality-of-life score (between-group difference in change, 0.8 points; 95% CI, −0.1 to 1.7), the EQ-5D-3L visual analogue scale (between-group difference in change, 8 points; 95% CI, −5 to 16), or the score on the descriptive system of the EQ-5D-3L (between-group difference in change, 0.8 points; 95% CI, −0.4 to 2.1) (Table 2).

DISCUSSION

This single-center, nonblinded, randomized trial, which was stopped early for efficacy, showed that compression therapy resulted in a lower incidence of recurrent cellulitis than conservative treatment in adults with chronic edema of the leg. This result supports expert opinion, but data from trials are limited.[2,3,13,14] The results of the analyses of hospitalization for cellulitis and of the change in leg volume from baseline were in the same direction as those of the primary outcome, but the lack of a prespecified plan for adjustment for multiple comparisons of secondary outcomes precludes clinical conclusions from these data. However, most quality-of-life measures did not differ substantially between the trial groups. Because the trial was stopped after the interim analysis, we were not able to report data on the 3-year effect of compression therapy on leg volume, as we had intended.

A Cochrane review showed that antibiotics

Table 2. Primary and Secondary Outcomes.

Outcome	Compression (N=41)	Control (N=43)	Between-Group Difference	Hazard Ratio or Relative Risk (95% CI)
Primary outcome: recurrence of cellulitis*				
No. (%)	6 (15)	17 (40)	11 (25)†	0.23 (0.09 to 0.59)‡
Relative risk (95% CI)				0.37 (0.16 to 0.84)§
Secondary outcomes¶				
Hospitalization for cellulitis — no. (%)*	3 (7)	6 (14)	3 (7)†	0.38 (0.09 to 1.59)
Mean change in leg volume at 12 mo‖**				
Change in volume (95% CI) — ml	−181 (−256 to −106)	60 (−38 to 159)	−241 (−365 to −117)	
Percent change (95% CI)	−4.3 (−5.8 to −2.9)	1.3 (−0.6 to 3.3)	−5.7 (−8.1 to −3.2)††	
Mean change in LYMQOL score at 12 mo (95% CI)‖‡‡				
Combined score	−0.5 (−0.6 to −0.4)	−0.2 (−0.3 to 0.02)	−0.3 (−0.6 to −0.1)	
Quality-of-life assessment	0.5 (−0.1 to 1.1)	−0.3 (−1.1 to 0.4)	0.8 (−0.1 to 1.7)	
Mean change in EQ-5D-3L score at 12 mo (95% CI)‖§§				
Visual analogue scale	−1 (−9 to 7)	−9 (−20 to 2)	8 (−5 to 16)	
Descriptive system	−0.3 (−0.9 to 0.4)	−1.1 (−2.2 to 0.01)	0.8 (−0.4 to 2.1)	

* Only data collected before the interim analysis were included in the analysis of recurrence of cellulitis and of hospitalization for recurrence of cellulitis.
† Shown is the difference between the control group and the compression group in the number of participants and the difference in percentage points.
‡ P=0.002.
§ P=0.02. The post hoc analysis of relative risk was performed because the proportional-hazards assumption was not met.
¶ Confidence intervals for secondary outcomes have not been corrected for multiple comparisons, and no clinical inferences can be made from these data.
‖ For this outcome, data were collected for participants in the control group until they crossed over to the compression group; data were collected for participants in the compression group until the last participant in the control group had crossed over. The mean change (slope) was estimated with the use of mixed-effects linear models that included baseline data and all available follow-up data.
** Change in leg volume was calculated on the basis of the change from the original volume measure of the same leg at the initial assessment. The contralateral leg was not used as a comparison for ipsilateral edema.
†† The value is the difference in percentage points.
‡‡ The quality-of-life measure for limb lymphedema (LYMQOL) has two components that are assessed separately: a quality-of-life score (scores range from 0 to 10, with higher scores indicating better quality of life) and a combined score that encompasses four domains (symptoms, appearance, function, and mood), each scored at four levels (not at all, a little, quite a bit, or a lot; combined scores range from 4 to 16, with lower scores indicating better quality of life).
§§ The EuroQol Group 5–Dimensions 3-Level scale (EQ-5D-3L) has two components that are assessed separately: a visual analogue scale that assesses the overall health state (scores range from 0 [worst imaginable health state] to 100 [best imaginable health state]) and a descriptive system that assesses five dimensions of quality of life (mobility, personal care, usual activities, pain and discomfort, and anxiety and depression) at three levels (no problems, some problems, or extreme problems); total scores for the descriptive system range from 5 to 15, with lower scores indicating better quality of life.

were the only prophylactic treatments for cellulitis of the leg that have been supported by randomized trials.[5] However, patients with preexisting edema, multiple previous episodes of cellulitis (≥3 episodes), or a high BMI (≥33) were less likely to benefit from antibiotic prophylaxis than other patients with cellulitis.[4] All participants in our trial had one or more risk factors that are predictive of antibiotic prophylaxis failure: all had preexisting edema, 79% had a BMI of 33 or greater, and 26% had had three or more episodes of cellulitis in the 2 years before the trial. We found that compression therapy reduced cellulitis recurrence in the participants in our trial, who were at risk for failure of antibiotic prophylaxis.

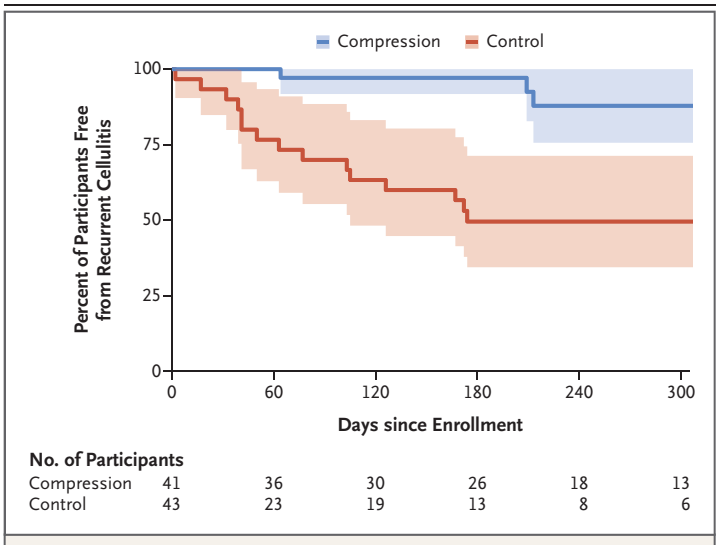

Figure 2. Freedom from Recurrence of Cellulitis over Time.

Shown are the Kaplan–Meier estimates of the freedom from recurrence of cellulitis in the compression group and the control group. The shaded areas indicate 95% confidence intervals. The median follow-up was 186 days.

Prevention of cellulitis by means of prophylactic antibiotics can cause side effects,[5] and the bacterial species precipitating cellulitis is usually unidentifiable,[23] which hinders targeted antibiotic prophylaxis.[24] In comparison, long-term use of compression therapy has been recommended[15] and has shown benefits in controlling edema in patients with chronic edema of the leg[20,25,26]; in addition, its efficacy is not related to the causative bacterial species. Long-term use of compression therapy has the additional potential advantages of managing chronic venous insufficiency,[27] venous ulcers,[16,28] and skin conditions (e.g., hyperkeratosis),[29,30] which are all common in patients with chronic edema. Furthermore, compression therapy is the primary treatment for lipodermatosclerosis, a condition that is often misdiagnosed as cellulitis[31] and for which antibiotic treatment is ineffective.

The mechanism by which compression therapy prevents recurrent cellulitis is not known. The relationship between chronic edema and cellulitis is considered to be multifactorial[32]: chronic edema provides a medium for bacterial growth,[32] altered lymphatic function and decreased lymphatic drainage can impair the immune response to pathogens,[33,34] and chronic edema can impair skin integrity,[30] increasing susceptibility to entry of bacteria through the skin.[32] Compression therapy could potentially decrease the risk of cellulitis by lessening edema, improving immune response and skin integrity, and providing physical protection for the skin. Future studies could explore the role of these mechanisms in cellulitis associated with chronic edema of the leg.

A potential source of bias in this trial is the fact that assessors and participants were aware of the trial-group assignments. Although the trial assessors, who were lymphedema therapists, had no influence on making the diagnosis of cellulitis, medical practitioners external to the trial who diagnosed cellulitis could have been influenced by the participants, who were aware of their trial-group assignments. The trial assessors also requested an early review of trial results because they anecdotally reported outcomes that favored the compression group, and this could also have introduced bias. With respect to measurement of leg volume, the calibrated perometer was used to mitigate the risk of bias because assessors were aware of the trial-group assignments. Difficulty in applying and removing compression garments is often a barrier to adherence to compression therapy; however, in our trial, 88% of the participants wore their garments 4 or more days per week. This high adherence may have been the result of support from experienced clinicians and may limit generalizability of our findings to other settings in which access to specialist lymphedema physiotherapists is not available.

Other trial limitations include the short duration of follow-up and possible misdiagnosis of cellulitis by medical practitioners. Although misdiagnosis of cellulitis is common,[35] this trial aimed to reflect standard clinical practice, and we accepted the diagnosis of cellulitis as determined by medical practitioners. The point estimates of differences in effect sizes between trial groups are imprecise because of the small size of the trial and because the trial was stopped early with post hoc stopping rules. The time to recurrence of cellulitis was reported by the participants; therefore, the precise time to recurrence may have varied by a few days or longer because the participants' recollection may not have been accurate.

This small, single-center, unblinded trial showed that compression therapy prevented the recurrence of cellulitis in patients with chronic

edema and a history of two or more previous episodes of cellulitis. Larger and longer trials are necessary in order to determine the effect of compression therapy on the recurrence of cellulitis, especially in settings without access to specialized lymphedema services.

Supported by Calvary Public Hospital Bruce, which funded the clinician time to initiate and manage the trial.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Robert Fleet for conducting the statistical analysis for the interim analysis and for participating as a member of the independent data monitoring committee; Angie Fearon and Jeremy Witchalls for participating as members of the independent data monitoring committee; Ming Ling for assistance with obtaining and refining the recruitment data; and the Calvary Public Hospital Bruce Lymphedema Team and Administration Team (especially Gemma Arnold, Marie-Michelle Coulombe, Emma May, Abby Benton, Caitlin Norris, Joshua Pogson, Alicia Palmer, Nievelle Chand, Sarah Toohey, Ashlee Cashion, and Bhavleen Singh) for assisting with data collection and trial administration.

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