Tremfya® ▼
(guselkumab)

Demonstrated sustained relief in Psoriasis at 5 years and in Psoriatic Arthritis at 2 years*[1,2]

COMPLETE SKIN CLEARANCE

- **At Week 16:** PASI 100 achieved in more than 1/3 of PsO patients treated with TREMFYA®.†[3]
- **Long term:** PASI 100 response rate of over 50% at Week 52 sustained at 5 years in PsO patients treated with TREMFYA®.†[1]

RAPID JOINT EFFICACY

- **At Week 4:** ACR20 achieved in 20% of PsA patients treated with TREMFYA®.[2]
- **Long term:** 74% ACR20 response rate seen at 1 year and sustained at 2 years in PsA patients treated with TREMFYA®.¶[2,4]

PROVEN DURABILITY

- Most patients who started on TREMFYA®, stayed on TREMFYA® long-term.[2,5]

To access educational videos, clinical papers, patient support and more visit **https://www.janssenmedicalcloud.co.uk/** or scan the QR code.

*Sustained improvements in psoriasis disease severity (as measured by PASI 90 and PASI 100 scores) and sustained improvements in psoriatic arthritis disease severity (as measured by ACR scores, HAQ-DI scores and resolution of enthesitis and dactylitis).[1,2] †PASI 100 analysis not part of the statistical analysis plan. 37.4% of patients treated with TREMFYA® achieved PASI 100 at Week 16 (n=329) vs 0.6% of patients treated with placebo (n=174; p<0.001; Non-responder imputation [NRI]).[3] ‡Patients achieving PASI 100 at Week 52: 50.5% (Treatment failure rules [TFR]), 51.3% (As observed), and 47.1% (NRI). In patients randomised to TREMFYA® at baseline. Patients achieving PASI 100 at Week 252: 51% (TFR), 52.8% (As observed) and 39.5% (NRI).[1] ¶In patients treated with TREMFYA® q8w. 74.6% (n=248) of TREMFYA® q8w patients achieved ACR20 at 1 year, and 74% (n=248) of TREMFYA® q8w patients achieved ACR20 at 2 years (NRI).[2,4] Complete skin clearance: Psoriasis Area and Severity Index [PASI] 100.[6] ACR20 – 20% improvement in a set of core measures: tender joint count, swollen joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's assessment of physical function, patient's assessment of physical function and acute-phase reactant value.[7] Durability, also known as patient retention or drug survival, is a combination of efficacy, safety, tolerability and patient satisfaction or preference.[8] VOYAGE 1 was a Phase 3, double-blind, placebo- and active comparator-controlled clinical trial that evaluated the efficacy and safety of TREMFYA® in patients with moderate-to-severe plaque psoriasis.[1] DISCOVER-2 was a Phase 3, double-blind, multi-centre, placebo-controlled clinical trial that evaluated the efficacy and safety of TREMFYA® in bio-naïve patients with active PsA.[9] TREMFYA® is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy.[10] TREMFYA®, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.[10]

References: 1. Griffiths CEM, et al. Maintenance of Response Through 5 Years of Continuous Guselkumab Treatment: Results From the Phase 3 VOYAGE 1 Trial. Presented at the 16th Annual Coastal Dermatology Symposium. October 15-16, 2020. **2.** McInnes IB, et al. Arthritis Rheumatol. 2021 Nov 1. doi: 10.1002/art.42010. **3.** Blauvelt A, et al. J Am Acad Dermatol 2017;76:405-417. **4.** McInnes IB, et al. Arthritis Rheumatol. 2021;73:604-616. **5.** Blauvelt A, et al. J Am Acad Dermatol 2021;S0190-9622:02816-4. **6.** Strober B, et al. J Am Acad Dermatol 2016;75:77-82.e7. **7.** Felson DT, LaValley MP. Arthritis Res Ther 2014;16:101. **8.** Geale K, et al. Rheumatol Adv Pract 2020;4:rkaa070. **9.** Mease PJ, et al. Lancet 2020;395:1126-1136 (Including supplementary appendix). **10.** TREMFYA® (guselkumab) 100 mg Summary of Product Characteristics.

ACR, American College of Rheumatology; **HAQ-DI**, Health Assessment Questionnaire - Disability Index; **PASI**, Psoriasis Area and Severity Index; **PsA**, psoriatic arthritis; **PsO**, psoriasis; **q8w**, every 8 weeks.

Tremfya▼ 100 mg solution for injection in pre-filled pen
PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): Guselkumab
Please refer to Summary of Product Characteristics (SmPC) before prescribing. **INDICATION(S):** Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Treatment of active psoriatic arthritis in adult patients, alone or in combination with methotrexate, who have had an inadequate response or have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. **DOSAGE & ADMINISTRATION:** For use under guidance/supervision of physician experienced in diagnosis and treatment of conditions for which Tremfya is indicated. Subcutaneous injection. Avoid areas showing psoriasis. **Adults:** For both indications, 100 mg at weeks 0 and 4, followed by maintenance dose every 8 weeks. In the case of psoriatic arthritis, for patients at high risk for joint damage according to clinical judgement, consider a dose of 100 mg every 4 weeks. Consider discontinuation if no response after 16 weeks of treatment for plaque psoriasis and after 24 weeks for psoriatic arthritis. **Children:** No data available in children/adolescents <18 years. **Elderly:** No dose adjustment required, limited information in subjects aged ≥ 65 years, very limited information > 75 years. **Renal & Hepatic impairment:** Not studied. **CONTRAINDICATIONS:** Serious hypersensitivity to active substance or excipients; clinically important, active infection. **Refer to SmPC for full list of excipients. SPECIAL WARNINGS & PRECAUTIONS:** ***Infections:*** Potential to increase risk. If signs/symptoms of clinically important chronic/acute infection occur, monitor closely and discontinue Tremfya until resolved. ***Tuberculosis:*** Evaluate patients for TB pre-treatment; monitor for signs/symptoms of active TB during and after treatment. Consider anti-TB therapy prior to Tremfya if past history of latent/active TB and adequate treatment course not confirmed. ***Serious hypersensitivity reaction:*** Includes anaphylaxis. Some serious hypersensitivity reactions occurred several days after treatment and included urticaria and dyspnoea. If occurs, discontinue Tremfya immediately and initiate appropriate therapy. ***Hepatic Transaminase Elevations:*** An increased incidence of liver enzyme elevations has been observed in patients treated with Tremfya q4w compared to patients treated with Tremfya q8w or placebo. When prescribing Tremfya q4w in psoriatic arthritis, consider evaluating liver enzymes at baseline and thereafter according to routine patient management. If increases in ALT or AST are observed and drug-induced liver injury is suspected, Tremfya should be temporarily interrupted until this diagnosis is excluded. ***Immunisations:*** Consider completing all appropriate immunisations prior to Tremfya. Do not use live vaccines concurrently with Tremfya; no data available; before live vaccination, withhold Tremfya for at least 12 weeks and resume at least 2 weeks after vaccination. **SIDE EFFECTS: Very common:** Respiratory tract infection. **Common:** headache, diarrhoea, arthralgia, injection site reactions, transaminases increased. **Other side effects:** hypersensitivity, anaphylaxis, rash, gastroenteritis, herpes simplex infections, tinea infections, neutrophil count decreased, urticaria. **Refer to SmPC for more detail on side effects. PREGNANCY:** Avoid use of Tremfya; no data. Women of childbearing potential should use effective contraception during and for at least 12 weeks after treatment. **LACTATION:** It is unknown whether guselkumab is excreted in human milk. A decision should be made to discontinue, or abstain from initiating treatment with Tremfya taking into account the benefit of breast-feeding to the child and the benefit of Tremfya therapy to the woman. **INTERACTIONS:** No dose adjustment when co-administering with CYP450 substrates. Concomitant immunosuppressive therapy or phototherapy not evaluated. **Refer to SmPC for full details of interactions. LEGAL CATEGORY:** Prescription Only Medicine (POM) **PRESENTATIONS, PACK SIZES, MARKETING AUTHORISATION NUMBER(S) & BASIC NHS COSTS**

PRESENTATIONS	PACK SIZES	MARKETING AUTHORISATION NUMBER(S)	BASIC NHS COSTS
Pre-filled pen (100mg)	X 1	NI: EU/1/17/1234/002 GB: PLGB 00242/0665	£2250

MARKETING AUTHORISATION HOLDER: Northern Ireland: Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgium. Great Britain: Janssen-Cilag Limited, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, UK **FURTHER INFORMATION IS AVAILABLE FROM:** Janssen-Cilag Limited, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, UK. Prescribing information last revised: June 2021

Adverse events should be reported. ▼This medicinal product is subject to additional monitoring and it is therefore important to report any suspected adverse events related to this medicinal product. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Janssen-Cilag Limited on 01494 567447 or at dsafety@its.jnj.com.

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Cellulitis in chronic oedema of the lower leg: an international cross-sectional study

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Conflicts of interest
See Appendix for full details.

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Summary

Background Cellulitis and chronic oedema are common conditions with considerable morbidity. The number of studies designed to assess the epidemiology of cellulitis in chronic oedema is scarce.

Objectives To investigate the prevalence and risk factors of cellulitis in chronic leg oedema, including lymphoedema.

Methods A cross-sectional study included 40 sites in nine countries during 2014–17. Adults with clinically proven unilateral or bilateral chronic oedema (oedema > 3 months) of the lower leg were included. The main outcome measures were frequency and risk factors for cellulitis within the last 12 months.

Results Out of 7477 patients, 15·78% had cellulitis within the last 12 months, with a lifetime prevalence of 37·47%. The following risk factors for cellulitis were identified by multivariable analysis: wounds [odds ratio (OR) 2·37, 95% confidence interval (CI) 2·03–2·78], morbid obesity (OR 1·51, 95% CI 1·27–1·80), obesity (OR 1·21, 95% CI 1·03–1·41), midline swelling (OR 1·32, 95% CI 1·04–1·66), male sex (OR 1·32, 95% CI 1·15–1·52) and diabetes (OR 1·27, 95% CI 1·08–1·49). Controlled swelling was associated with a reduced risk (OR 0·59, 95% CI 0·51–0·67). In a subgroup analysis, the risk increased with the stage of oedema [International Society of Lymphology, stage II OR 2·04 (95% CI 1·23–3·38) and stage III OR 4·88 (95% CI 2·77–8·56)].

Conclusions Cellulitis in chronic leg oedema is a global problem. Several risk factors for cellulitis were identified, of which some are potentially preventable. Our findings suggest that oedema control is one of these. We also identified that advanced stages of oedema, with hard/fibrotic tissue, might be an important clinical indicator to identify patients at particular risk.

What is already known about this topic?

- Chronic oedema has many different causes and is a frequent but neglected healthcare problem.
- The association between chronic oedema and cellulitis is known, but few studies have clinically evaluated the size of the problem and the risk factors.
- Guidelines suggests that control of oedema is important to reduce the risk of recurrent cellulitis, but the evidence is limited.

What does this study add?

- Cellulitis in chronic leg oedema is common in all countries and types of health facilities.
- Wounds, obesity, midline swelling, male sex and diabetes were independently associated with a recent episode of cellulitis (within the last 12 months).
- Severe stages of oedema were associated with cellulitis, while controlled swelling was associated with a reduced risk.
- Measures to improve the control of swelling may have a major effect on the incidence of cellulitis, being potentially preventable.

Cellulitis is a common bacterial infection of the dermis and subcutaneous tissue,[1] and can occur in any body site, lower limbs being affected in 70–80% of cases.[2] It is a common medical emergency, often leading to hospitalization, long-term morbidity and recurrent disease.[1] In 2018–19 cellulitis accounted for 1·4% of all emergency admissions in the UK,[3] and it has been reported that it is one of the leading causes of potentially preventable hospitalizations.[4]

Chronic oedema is also frequent, with an estimated prevalence of 38% in European hospitals,[5] and 57% of patients cared for by community nurses in the UK.[6] Yet, it is a neglected healthcare issue.[7] Chronic oedema is defined as oedema present for more than 3 months.[8] Traditionally, the term lymphoedema has been used for oedema resulting from a failure of the lymphatics, e.g. due to congenital malformation, cancer, injury or filariasis. However, recent research indicates the substantial role of the lymphatics in all chronic oedema, leading to the introduction of this umbrella term. Chronic oedema is often multifactorial and covers a wide range of pathologies including lymphoedema (primary and secondary), but also swelling due to venous insufficiency, immobility and obesity.[7]

A recent meta-analysis identified lymphoedema/chronic leg oedema as an independent risk factor for cellulitis [odds ratio (OR) 6·77, 95% confidence interval (CI) 3·46–13·27].[9] One of the reasons that the risk of cellulitis may be increased is due to the important role of the lymphatics in immunity.[10,11] Although both diseases are common, few studies have been designed to clinically examine the epidemiology of cellulitis in patients with chronic oedema. The objective of this study was to investigate the association of potential risk factors with the presence of cellulitis in patients with chronic leg oedema. The identification of preventable or modifiable risk factors could improve patient outcomes.

Methods

This is an international, multicentre, cross-sectional study, performed as part of LIMPRINT (Lymphoedema IMpact and PRevalence – INTernational Lymphoedema Framework), an epidemiology study designed to prospectively determine the impact and prevalence of chronic oedema within health services. Forty sites from nine countries participated between June 2014 and August 2017. Hospital (in- and outpatients) and community cases were included. Main outcome of interest was the presence of cellulitis (yes/no) in the sites affected by chronic leg oedema within the last 12 months, and its relation to potential risk factors. Each country and study centre gained the appropriate approvals from the relevant Ethical Review Committee and other research and service development committees.

Chronic oedema

Chronic oedema is defined as oedema present for more than 3 months and affecting one or more areas of the body [limbs, hands/feet, upper body (breast/chest wall, shoulder, back), lower body (buttocks, abdomen), genitalia (scrotum, penis, vulva), head, neck or face].[8] Oedema was confirmed using the validated 'Pitting Oedema Test' and Stemmer's sign (a positive Stemmer's sign: a skin fold that cannot be pinched at the base of the second toe, which is diagnostic of lymphoedema). Patients with long-standing chronic nonpitting oedema with fibrosis were also included.[12] The duration was determined from medical records and through the patient or caregiver. The severity was judged by palpation and clinical evaluation of the skin, using International Society of Lymphology (ISL) staging,[13] originally developed for lymphoedema:

Stage I: Early onset, with an accumulation of tissue oedema that decreases with limb elevation; the oedema may be pitting.

Stage II: Limb elevation alone rarely reduces swelling and pitting is manifested.

Stage III: The tissue is fibrotic (hard) and pitting is absent; skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits and warty overgrowths develop.

Cellulitis

Cellulitis is defined as an acute onset of soft-tissue erythema, warmth and tenderness that rapidly resolves with antibiotics, most often caused by *Streptococcus pyogenes* and/or *Staphylococcus aureus* (to a lesser extent). Erysipelas is a similar infection, but typically affects the more superficial part of the skin compared with cellulitis. The terms are often used interchangeably,[1] and are considered as one clinical issue in this manuscript. The current presence or history of cellulitis were confirmed by a

combination of physical examination, interview with the patient and/or review of the medical records by teams of clinicians, all of which included experts in lymphology.

Study population

The study population comprised adults 18 years of age and older, with clinically proven unilateral or bilateral chronic leg oedema (regardless of the underlying cause), who could understand the study and give informed consent according to ethical standards. Cases were excluded if unwilling or unable to participate, receiving end-of-life care or if judged as not in the patient's best interest.

Data collection

The methods have been published previously.[14] In brief, a standardized core tool was used for all participants; it was developed by an international expert panel and included both a questionnaire and a physical examination. An expert review deemed the tool to be highly accurate.[14] Data were collected by trained healthcare professionals. Lymphoedema specialists confirmed the underlying chronic oedema classification and the diagnosis of cellulitis. An additional tool was used in some centres with the appropriate expertise for undertaking the staging procedure (ISL). All sites followed the international study protocol and complied with standard operating procedures. In nine lymphoedema specialist centres, data using the LIMPRINT core tool were obtained from clinical records of all patients.[15]

Variables

There are no internationally agreed definitions on the outcome on chronic oedema management. In this study 'control of swelling' was a subjective judgement by the investigator based on the clinical observation of the limb, clarified with the caregiver and if necessary with the lead physician within each service.[16] It was assessed as either present, absent or 'don't know', at the time of clinical assessment. The type (or absence) of treatment was noted including skin care, exercise, manual lymph drainage, types of compression, antibiotics, psychological support and surgical treatments. Data included demographics and relevant comorbidities. Body mass index (BMI) was estimated according to World Health Organization categories as either underweight (BMI < 20), normal weight (BMI 20–30), obese (BMI 30–40) or morbidly obese (BMI > 40). The site of chronic oedema was collected using a body map where the upper and lower extremities, trunk including genitals (collectively termed midline swelling), face and neck were recorded. The oedema was further classified as either primary (congenital) or secondary (acquired), and whether related to cancer or not. Cancer-related oedema was classified as either caused by treatment and/or due to metastatic disease. Noncancer oedema was classified as due to clinically assessed venous disease (including confirmation by ultrasound), obesity, immobility, lymphatic filariasis and/or 'other'. Duration of oedema and leg mobility was documented. Wounds defined as 'loss of intact skin' were determined through clinical examination (wound classification will be published elsewhere). In selected centres, the severity of oedema was also assessed using the ISL staging tool.

Statistics

Statistical analyses were performed in Stata 12 (Statacorp; College Station, TX, USA). Due to the explorative study design, a formal sample size determination was not performed. A sample of over 5000 patients was expected to reveal the major factors associated with cellulitis. The principal analysis examined the binary outcome (history vs. no history of cellulitis within the previous 12 months). Factors tested for an association with the outcome were demographics, medical history and leg and swelling characteristics. These variables were chosen as they were believed to be potentially associated with the outcome and could be reliably collected in an international study like this. The principal analysis used logistic regression. Univariate comparisons were followed by a multivariable model, using a stepwise elimination until all factors remaining had an α of $< 0{\cdot}05$. Results were presented as ORs and 95% CIs. A similar analysis examined the severity of chronic oedema in a subgroup of 966 patients. Missing data were not imputed and therefore remained missing.

Results

Characteristics of countries, sites and patients

From those included in the Limprint database, 10 127 patients undertook the core questionnaire, had a site of swelling and were 18 years of age or older; 7722 (76·25%) of these were identified with leg oedema and were included in this study. Of these patients with leg oedema, 7477 (96·8%) patients gave a response to the question about whether they had experienced a recent (< 12 months) history of cellulitis. Of the cohort (with or without cellulitis), 61·87% had well-controlled chronic oedema. Patient characteristics are presented in Table 1. In total, 40 sites from nine countries participated, including Australia, Canada, Denmark, France, Ireland, Italy, Japan, Turkey and the UK (Table 2). These included specialist lymphoedema services (73·4%), outpatient acute hospitals (9·0%), hospitalized cases (8·6%), community nursing (1·2%), elderly care residential homes (0·3%), nursing homes (0·1%) and other (7·3%).

General risk factors

On univariate analysis statistically significant associations were found between recent cellulitis and diabetes (OR 1·56), male sex (OR 1·47), morbid obesity (OR 1·56), obesity (OR 1·19), chair-bound patients (OR 1·39), peripheral arterial disease (OR 1·37) and heart failure/ischaemic heart disease (OR 1·25). Age was weakly associated ($P = 0{\cdot}12$); see Table 3.

Table 1 Demographics of the patients with chronic leg oedema for whom information on presence or absence of cellulitis is available (n = 7477)[a]

Characteristic(s)	Number of patients (%)[b]	Missing data
Age, mean years (SD)	65·05 (16·36)	2
Female	5265 (70·42)	0
Weight		11
Normal weight	3120 (41·79)	
Underweight	164 (2·20)	
Obese	2631 (35·24)	
Morbidly obese	1551 (20·77)	
Concomitant disease		
Diabetes	1379 (18·44)	0
Heart failure/ischaemic heart disease	1184 (15·84)	0
Facility		0
Hospital-based cases	7018 (93·86)	
Community cases	125 (1·67)	
Other	334 (4·47)	
Classification of chronic oedema		
Primary	1396 (18·83)	65
Secondary	6016 (81·17)	
Related to cancer or its treatment	1057 (17·63)	22
Noncancer	4937 (82·37)	
Venous disease[c]	2421 (49·12)	
Immobility[c]	1847 (37·47)	
Obesity[c]	1478 (29·99)	
Filariasis[c]	8 (0·22)	
Unilateral leg oedema	1861 (24·89)	0
Bilateral leg oedema	5616 (75·11)	
ISL scale (n = 966)[d]		0
I	237 (24·53)	
II	549 (56·83)	
III	180 (18·63)	
Duration of leg oedema		11
< 1 year	833 (11·16)	
1–2 years	739 (9·90)	
2–5 years	1561 (20·91)	
> 5–10 years	1685 (22·57)	
> 10 years	2648 (35·47)	
Mobility		9
Normal	4203 (56·28)	
Walking aid	2466 (33·02)	
Chair-bound	691 (9·25)	
Bed-bound	108 (1·45)	
Concurrent swelling		
Upper limb	360 (4·81)	0
Midline	586 (7·84)	0
Presence of a leg wound	1129 (15·13)	17
Treatment with compression therapy		20
Compression garment	5101 (68·41)	
Multilayer bandage	1888 (25·32)	
Compression wrap	668 (8·96)	
At least one of the above	5804 (77·83)	
No compression	1653 (22·17)	
Good control of swelling	4314 (61·87)	504[e]
Life history of cellulitis	2802 (37·47)	
Antibiotics	448 (6·01)	20
Hospitalized cases due to cellulitis within the last 12 months	368 (4·95)	47

[a]Numbers indicate the actual number of recorded values excluding missing data. [b]%, unless otherwise noted; [c]breakdown and percentages derived from 'present' values shown in Table 4; [d]ISL scale, International Society of Lymphology scale (as described in Patients and Methods) – this was performed only in those centres with the appropriate expertise for undertaking the staging procedure; therefore, missing data is regarded as = 0; [e]Includes missing and uncertain values.

Local risk factors

On univariate analysis, wounds were identified as a statistically significant risk factor (OR 2·75). Secondary lymphoedema was associated with cellulitis when compared with primary lymphoedema (OR 1·25), but the risk was not related to whether the oedema was caused by cancer or its treatment or a noncancer cause. Of the other factors only venous disease (OR 1·21) showed a positive association, and concomitant midline swelling (OR 1·30). Control of swelling was associated with a significantly lower risk (OR 0·51) (Table 4).

Independent risk factors

Factors remaining after multivariable analysis (logistic regression) were wounds (OR 2·37), morbid obesity (OR 1·51), obesity (OR 1·21), midline swelling (OR 1·32), male sex (OR 1·32) and diabetes (OR 1·27). Patients with controlled swelling had a markedly lower risk of cellulitis, OR 0·59 (95% CI 0·51–0·67, P < 0·001) (see Table 5).

Frequency of cellulitis

Of the patients with chronic oedema of the lower leg 37·47% (2802 of 7477) experienced at least one episode of cellulitis during their lifetime. In total, 15·78% (n = 1180) had a history of cellulitis within the last 12 months, of whom 368 (31·2%) were hospitalized. The frequency of recent cellulitis ranged from 13·94% in the UK to 38·24% in Canada (see Table 2). The difference is likely explained by the type of facility.

In those assessed for the severity of the chronic oedema (n = 966), the frequency of a recent history of cellulitis changed with ISL stage, affecting 11·56% with ISL stage I, 50·75% in stage II and 37·69% in stage III (Table 6).

Severity of oedema

Severity of oedema (n = 966, Table 6) was significantly associated with cellulitis: ISL stage II OR 2·10 and stage III OR 6·65 compared with stage I, by univariate analysis. An

Table 2 History of lower leg cellulitis (< 12 months) in patients with chronic oedema by country

Country	Total number of patients with chronic oedema	History of cellulitis (< 12 months)	Percentage
UK	4714	657	13·94
France	347	49	14·12
Japan	82	14	17·07
Denmark	859	149	17·35
Italy	1065	211	19·81
Turkey	216	43	19·91
Australia	108	26	24·07
Ireland	18	5	27·78
Canada	68	26	38·24
Total	7477	1180	15·78

increased risk was also seen in hard (fibrotic) tissue vs. soft tissue (OR 2·85), and with a positive Stemmer's sign (OR 2·23). Even after adjustment for sex, obesity, diabetes, wounds, controlled swelling and midline swelling (n = 889, Table 6), ISL stage II yielded an OR of 2·04, and stage III an OR of 4·88, by multivariable analysis.

Discussion

This large study confirms that cellulitis is common in patients with chronic leg oedema. Of the patients studied, 15·78% had experienced at least one episode of cellulitis within the last 12 months, with a lifetime prevalence of 37·47%. The methodology adopted, with a physical examination, access to lymphoedema experts, use of international definitions and standard operating procedures, strengthens the validity of our data. The lifetime prevalence is higher than previously reported (7·95–35·7%), with direct comparison challenging due to methodological differences.[17–19]

Wounds, obesity, male sex, diabetes, midline swelling and, particularly, advanced stages of chronic oedema were independent risk factors for cellulitis, while control of swelling was associated with a lower risk. Although risk factors in cellulitis have been studied in a meta-analysis (identifying previous

Table 3 Explanatory variables for recent (< 12 months) cellulitis in patients with chronic oedema of the lower leg, by univariate analysis (n = 7477)[a]

Risk factor	No cellulitis, N (%)	Cellulitis, N (%)	OR (95% CI)	P-value
Sex				
Female	4517 (71·73)	748 (63·39)	1·00	
Male	1780 (28·27)	432 (36·61)	1·47 (1·29–1·66)	< 0·001
Age				
< 45 years	794 (12·61)	140 (11·87)	1·00	
45–64 years	1945 (30·89)	394 (33·42)	1·15 (0·93–1·42)	
65–74 years	1474 (23·41)	289 (24·51)	1·11 (0·89–1·38)	0·12
75–84 years	1389 (22·06)	251 (21·29)	1·02 (0·82–1·28)	
85 + years	694 (11·02)	105 (8·91)	0·86 (0·65–1·13)	
Obesity				
Normal weight	2694 (42·85)	426 (36·13)	1·00	
Underweight	136 (2·16)	28 (2·37)	1·30 (0·86–1·98)	
Obese	2213 (35·20)	418 (35·45)	1·19 (1·03–1·38)	
Morbidly obese	1244 (19·79)	307 (26·04)	1·56 (1·33–1·83)	< 0·001
Leg mobility				
Walks unaided	3570 (56·77)	633 (53·64)	1·00	
Walks with aid	2068 (32·89)	398 (33·73)	1·09 (0·95–1·24)	
Chair-bound	554 (8·81)	137 (11·61)	1·39 (1·14–1·71)	0·007
Bed-bound	96 (1·53)	12 (1·02)	0·70 (0·38–1·29)	
Diabetes				
Absent	5208 (82·71)	890 (75·42)	1·00	
Present	1089 (17·29)	290 (24·58)	1·56 (1·34–1·81)	< 0·001
Heart failure/ischaemic heart disease				
Absent	5332 (84·68)	963 (81·61)	1·00	
Present	965 (15·32)	217 (18·39)	1·25 (1·06–1·46)	0·008
Neurological disease				
Absent	5729 (91·17)	1067 (90·81)	1·00	
Present	555 (8·83)	108 (9·19)	1·04 (0·84–1·30)	0·69
Peripheral arterial disease				
Absent	6088 (96·68)	1127 (95·51)	1·00	
Present	209 (3·32)	53 (4·49)	1·37 (1·01–1·86)	0·044

[a]Numbers indicate the actual number of recorded values excluding missing data.

Table 4 Explanatory variables for cellulitis in patients with chronic oedema of the lower leg, by univariate analysis (n = 7477)[a]

Risk factor	No cellulitis, N (%)	Cellulitis, N (%)	OR (95% CI)	P-value
Swelling duration, n = 7466				
< 1 year	684 (10·88)	149 (12·64)	1·00	
1–2 years	645 (10·26)	94 (7·97)	0·67 (0·51–0·88)	
2–5 years	1337 (21·27)	224 (19·00)	0·77 (0·61–0·96)	0·015
5–10 years	1399 (22·25)	286 (24·26)	0·94 (0·75–1·17)	
> 10 years	2222 (35·34)	426 (36·13)	0·88 (0·72–1·08)	
Classification, n = 7412				
Primary	1208 (19·35)	188 (16·07)	1·00	
Secondary	5034 (80·65)	982 (83·93)	1·25 (1·06–1·48)	0·008
Secondary cause, n = 5994				
Cancer	897 (17·89)	160 (16·34)	1·00	
Noncancer	4118 (82·11)	819 (83·66)	1·11 (0·93–1·34)	0·25
Cancer cause, n = 1053[b]				
Cancer treatment				
Absent	125 (13·98)	13 (8·18)	1·00	
Present	769 (86·02)	146 (91·82)	1·83 (1·00–3·32)	0·046
Cancer metastasis				
Absent	789 (88·26)	149 (93·71)	1·00	
Present	105 (11·74)	10 (6·29)	0·50 (0·26–0·99)	0·042
Noncancer, n = 4929[c]				
Venous				
Absent	2125 (51·67)	383 (46·94)	1·00	
Present	1988 (48·33)	433 (53·06)	1·21 (1·04–1·40)	0·014
Immobility				
Absent	2585 (62·85)	497 (60·91)	1·00	
Present	1528 (37·15)	319 (39·09)	1·09 (0·93–1·27)	0·30
Obesity				
Absent	2952 (71·77)	499 (61·15)	1·00	
Present	1161 (28·23)	317 (38·85)	1·62 (1·38–1·89)	< 0·001
Concomitant arm swelling				
Absent	5990 (95·12)	1127 (95·51)	1·00	
Present	307 (4·88)	53 (4·49)	0·92 (0·68–1·24)	0·57
Concomitant midline swelling				
Absent	5824 (92·49)	1067 (90·42)	1·00	
Present	473 (7·51)	113 (9·58)	1·30 (1·05–1·62)	0·015
Leg wound, n = 7460				
Absent	5490 (87·36)	841 (71·51)	1·00	
Present	794 (12·64)	335 (28·49)	2·75 (2·38–3·19)	< 0·001
Control of swelling, n = 6973				
Not controlled	2082 (35·54)	577 (51·80)	1·00	
Controlled	3777 (64·46)	537 (48·20)	0·51 (0·45–0·58)	< 0·001

[a]Numbers indicate the actual number of recorded values excluding missing data. [b]Evidence of the type of cancer cause not given, n = 4.
[c]Filariasis was not included in this table due to small numbers; also, missing values, n = 8.

cellulitis, concurrent wounds, leg ulcers, excoriating skin diseases, tinea pedis, obesity and lymphoedema/chronic oedema as risk factors),[9] only one single-centre study has been specifically designed in patients with chronic oedema/lymphoedema.[20] Independent risk factors were percentage difference of circumference of the limb, 'food induced complications experiences', systolic blood pressure and primary lymphoedema. In contrast, we found that secondary lymphoedema was associated with cellulitis on univariate analysis, but it was not an independent risk factor.

Our most important findings were that control of swelling was associated with a significantly lower risk of cellulitis (OR 0·59) while advanced stages of chronic oedema were strong risk factors (ISL stage II: OR 2·04 and stage III: OR 4·88), assessed by multivariable analysis, indicating that cellulitis may be preventable. Measures to control the swelling and halt the progression into advanced stages, e.g. with appropriate compression garment, should be mandatory.

Chronic oedema management is already widely recognized as an adjuvant to antibiotic prophylaxis for recurrent cellulitis.[21,22] A randomized clinical trial (n = 84) in compression therapy significantly lowered the incidence of recurrence of cellulitis compared with conservative treatment, with a relative risk of 0·37 in favour of compression.[23] However, in our

Table 5 Logistic regression analysis. Independent risk factors associated with cellulitis of the lower leg in patients with chronic oedema (n = 6947)

	OR (95% CI)	P-value
Sex		
Female	1·00	
Male	1·32 (1·15–1·52)	< 0·001
Weight		
Normal weight	1·00	
Underweight	1·17 (0·78–1·82)	
Obese	1·21 (1·03–1·41)	
Morbidly obese	1·51 (1·27–1·80)	< 0·001
Diabetes		
Absent	1·00	
Present	1·27 (1·08–1·49)	0·003
Wound		
Absent	1·00	
Present	2·37 (2·03–2·78)	< 0·001
Midline swelling		
Absent	1·00	
Present	1·32 (1·04–1·66)	0·020
Control of oedema		
Not controlled	1·00	
Controlled	0·59 (0·51–0·67)	< 0·001

cohort only 48·2% of those with recent cellulitis had proper oedema control, highlighting the need to focus on this issue. A reduced incidence of cellulitis by implementation of compression therapy has been reported to decrease healthcare costs almost threefold over a 1-year period, mainly explained by a reduction of acute care costs.[24] Mechanisms of compression include reduced capillary filtration, increased lymphatic drainage and a downregulation of proinflammatory cytokines. Warty skin, venous eczema and occasionally fibrosis (especially seen in ISL stage III) can be reversed.[25,26] These conditions are reservoirs or entry points for microbes.

It is hypothesized that the risk of cellulitis is increased due to a local immune deficiency, with an ineffective transport of antigens to the lymph node. Lymph stasis may also facilitate bacterial growth and impede bacterial and toxin clearance.[27] Cellulitis also seems to impair the lymphatics. A single methicillin-resistant *Staphylococcus aureus* infection has been shown to inhibit lymphatic vessel contraction and flow long after infection clearance.[27] As oedema predisposes to cellulitis and cellulitis can impair the lymphatics, potential prophylactic interventions should target all steps in this vicious cycle.[11]

As expected, wounds were associated with cellulitis, as was obesity. Increased fat deposition in primary lymphoid organs leading to alterations of the leucocyte population might play a part.[28] Furthermore, decreased lymphatic transport, fewer lymphatic vessels, and changed architecture and smaller lymph nodes have been observed in obese mice.[29] We also found that males were 30% more likely to experience cellulitis than females, which has not been reported.[9] Male predominance may be due to behavioural and biological factors[30] with less-efficient antigen presentation, lower phagocytic activity and lower antibody production.[31]

Diabetes as a risk factor for cellulitis could not be confirmed in the previously mentioned meta-analysis,[9] perhaps due to a too-small sample size. However, our results are supported by a large, matched cohort study [type I diabetes OR 2·84 (95% CI 2·48–3·25); type II OR 2·03 (1·97–2·08)].[32] Abnormal neutrophil function and T-lymphocyte responses might come into play.[32] Proper foot care to prevent cellulitis is mandatory for all diabetics.

Table 6 Explanatory variables for cellulitis related to the severity of chronic leg oedema, a subgroup analysis (n = 966)

	No cellulitis, n (%)	Cellulitis, n (%)	OR 95%CI	P-value
Pitting				
Nonpitting	215 (28·0)	62 (31·2)	1·00	0·39
pitting	552 (72·0)	137 (68·8)	0·86 (0·61–1·21)	
Tissue quality				
Soft	575 (74·97)	102 (51·3)	1·00	< 0·001
Hard (fibrotic)	192 (25·0)	97 (48·7)	2·85 (2·07–3·93)	
Stemmer's sign (missing, n = 24)				
Negative	315 (42·0)	47 (24·5)	1·00	< 0·001
Positive	435 (58·0)	145 (75·5)	2·23 (1·56–3·20)	
ISL scale				
Stage I	214 (27·9)	23 (11·6)	1·00	< 0·001
Stage II	448 (58·4)	101 (50·8)	2·10 (1·30–3·39)	
Stage III	105 (13·7)	75 (37·7)	6·65 (3·94–11·20)	
ISL scale after adjustment[a] (n = 889)				
Stage I			1·00	< 0·001
Stage II			2·04 (1·23–3·38)	
Stage III			4·88 (2·77–8·56)	

ISL scale, International Society of Lymphology scale (as described in Patients and Methods). [a]ISL scale after adjustment for sex, obesity, diabetes, wound, control and midline swelling by logistic regression.

Being chair-bound was also a risk factor, which might be explained by the increased hydrostatic pressure and lack of use of the calf muscles, worsening the oedema. However, this association disappeared when correcting for other factors.

Limitations to our study need to be noted. Cellulitis is known for being easily misdiagnosed (up to 30·7% of cases).[33] Observer bias was minimized by the use of international definitions of cellulitis, standard operating procedures and training.[14] Recall bias was minimized by seeking information from the medical records.

Although recruitment was made from hospitals and community facilities, the majority of the patients were included from hospitals, potentially skewing our data towards more severe cases. Also, patients from developing countries were not included.

The assessment of 'control of swelling' was open to personal interpretation. However, data were excluded when the clinician was uncertain of the control status (n = 465) and access to lymphoedema teams assisted in increasing the accuracy of the decisions.

The lack of correction for prophylactic antibiotics might also influence our data. Although antibiotic use was recorded in 194 of 6283 (3·09%) with no cellulitis vs. 254 of 1174 (21·64%) with a recent history of cellulitis, this did not specify its use in prophylaxis, and may be the result of treating the acute infection. Lastly, one should keep in mind that a cross-sectional study is limited to an assessment at only one timepoint, indicating association but not causation.

In conclusion, our findings confirm that cellulitis in chronic leg oedema is a global problem. Although guidelines support the use of oedema control to prevent cellulitis (e.g. with compression therapy), a substantial number of those recruited had uncontrolled swelling. This study adds epidemiological evidence of what has been known anecdotally for a long time: that oedema control is associated with a lower risk of cellulitis. Wounds, warty skin and eczema, as often seen in advanced stages of oedema, are potential entry points and/or reservoirs for microbes, and can be prevented and treated by compression therapy. Prevention of deterioration of the oedema may have a significant effect on reducing the risk of cellulitis, and thereby reducing healthcare costs.

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Appendix Conflicts of interest

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