Cellulitis (MONDO:0005230): A Comprehensive Disease Characteristics Report

Summary

Cellulitis is a common acute bacterial infection of the deep dermis and subcutaneous tissue that arises from a "two-hit" combination of a skin-barrier breach and impaired lymphatic/venous drainage. In its most common (non-purulent) form it is predominantly caused by β-hemolytic streptococci, while purulent forms are typically driven by *Staphylococcus aureus* (including MRSA). Bacterial invasion of subcutaneous tissue, amplified by toxin-mediated cytolysis and a brisk innate inflammatory response, produces the cardinal clinical picture of poorly demarcated erythema, warmth, swelling (edema), pain, and tenderness — usually unilateral and most often affecting the lower leg. It is a clinical diagnosis with no gold-standard laboratory test; roughly one-third of patients admitted for "cellulitis" actually have a non-infectious mimic ("pseudocellulitis"), which drives substantial unnecessary antibiotic use and hospitalization.

The disease sits within a spectrum of skin and soft-tissue infections (SSTIs). At the mild end it overlaps with erysipelas (more superficial) and simple abscess; at the dangerous end it must be distinguished from **necrotizing fasciitis (NF)**, a surgical emergency. The two critical clinical decisions in cellulitis care are therefore (1) purulent vs. non-purulent (which determines whether empiric MRSA coverage is needed) and (2) cellulitis vs. necrotizing infection (which determines whether urgent surgery is required). Uncomplicated non-purulent cellulitis is treated with streptococcal-targeted β-lactams (e.g., cephalexin, dicloxacillin/flucloxacillin, penicillin); a landmark randomized trial showed that adding MRSA-active trimethoprim-sulfamethoxazole to cephalexin provides no benefit in uncomplicated disease.

Cellulitis is a large, rising, and costly public-health burden strongly linked to chronic edema and lymphedema. Recurrence is frequent and is driven by a self-reinforcing cycle in which each episode further damages lymphatics, worsening drainage and predisposing to the next episode. Two categories of prevention have robust randomized-trial support: **prophylactic low-dose penicillin V** (PATCH I trial: hazard ratio 0.55 for recurrence, number-needed-to-treat

5) and **compression therapy for chronic leg edema** (Webb NEJM trial: hazard ratio 0.23, stopped early for efficacy). This is not a genetic/Mendelian disease — there are no causal genes; "genetics" enters only through host susceptibility (e.g., diabetes, immune impairment) and pathogen virulence genetics (e.g., group A *Streptococcus* covR/covS regulatory mutations and toxins SpeB and streptolysin S).

Section 1 — Disease Information

Overview. Cellulitis is an acute, spreading bacterial infection of the deep dermis and subcutaneous fat. Clinically it presents as an area of expanding erythema with warmth, edema, and tenderness, frequently accompanied by systemic features (fever, malaise) in more severe cases. **Erysipelas** is a closely related, more superficial variant involving the upper dermis and superficial lymphatics, classically with a raised, sharply demarcated border; in much of the clinical literature "cellulitis" and "erysipelas" are grouped together (as in the PATCH prophylaxis trials and the US burden analyses). The disease is best understood as the confluence of two prerequisites: **a portal of entry** (barrier breach) and **impaired local host drainage** (edema/lymphedema/venous insufficiency).

Key identifiers.

Resource	Identifier
MONDO	MONDO:0005230
ICD-10	L03 (Cellulitis and acute lymphangitis); e.g., L03.11 cellulitis of lower limb; periorbital/orbital variants coded under H00–H05
ICD-11	1B70 (Cellulitis)
MeSH	D002481 "Cellulitis"
SNOMED CT	128045006 (Cellulitis)
OMIM / Orphanet	Not applicable — cellulitis is an acquired infectious disease, not a Mendelian disorder; no OMIM phenotype entry, not a rare disease with an Orphanet number

Synonyms / alternative names. Cellulitis; bacterial cellulitis; skin and soft-tissue infection (as a parent category); erysipelas (superficial variant, often grouped); acute bacterial skin and skin-structure infection (ABSSSI — the regulatory term used in clinical trials); phlegmon (for the more diffuse suppurative form). Site-specific named entities include **periorbital (preseptal) cellulitis**, **orbital (postseptal) cellulitis**, and diabetic-foot cellulitis.

Data source type. The evidence base for cellulitis is drawn overwhelmingly from **aggregated disease-level resources** — randomized controlled trials, systematic reviews/meta-analyses, population-based case-control studies, and national administrative datasets (e.g., US National Emergency Department Sample, National Inpatient Sample) — rather than from individual-patient genomic/EHR mining. This reflects its nature as a common acquired infection rather than a rare genetic disorder.

Section 2 — Etiology

Primary cause: infectious. Cellulitis is caused by bacteria that gain access to the deep dermis/subcutaneous tissue. The dominant organisms differ by clinical subtype:

- **Non-purulent cellulitis → β-hemolytic streptococci** (predominantly group A *Streptococcus pyogenes*, but also groups B, C, G). This is **Finding F001**. Two 2026 narrative reviews concur that "*β-hemolytic streptococci are the most common cause of non-purulent cellulitis*" (PMID: 42711142) and that "*Non-purulent SSTI is most commonly associated with beta-haemolytic streptococci, while purulent SSTI is typically associated with Staphylococcus aureus*" (PMID: 42727947).
- **Purulent cellulitis / abscess → *Staphylococcus aureus*, including MRSA.**
- **Special hosts/exposures** broaden the microbiology: diabetic foot infection can be polymicrobial (gram-negative aerobes and anaerobes) (PMID: 27377687); water/marine exposure raises *Vibrio*/*Aeromonas*; endemic-area/diabetic patients can develop *Burkholderia pseudomallei* (melioidosis) mimicking necrotizing infection (PMID: 41580634); immunocompromised patients may present with fungal mimics such as primary cutaneous cryptococcosis (PMID: 42240944).

Risk factors (environmental/host). Finding F002 synthesizes the strongest quantitative evidence. A systematic review/meta-analysis of 6 case-control studies (PMID: 27864837) and a population-based case-control study of 29,062 pairs (PMID: 29427797) establish the following:

Risk factor	Odds ratio (95% CI)	Source
Previous cellulitis	OR 40.3 (22.6–72.0)	P 27864837
Wound	OR 19.1 (9.1–40.0)	P 27864837
Current leg ulcer	OR 13.7 (7.9–23.6)	P 27864837
Lymphoedema / chronic leg oedema	OR 6.8 (3.5–13.3)	P 27864837
Excoriating skin disease	OR 4.4 (2.7–7.1)	P 27864837
Tinea pedis	OR 3.2 (1.9–5.3)	P 27864837
Varicose veins	AOR 2.95 (2.50–3.48)	P 29427797
Tinea pedis	AOR 3.05 (1.45–6.42)	P 29427797
Lymphoedema	AOR 2.65 (1.71–4.10)	P 29427797
Obesity (BMI >30)	AOR 2.05	P 29427797
Saphenous vein harvest	AOR 1.74	P 29427797
Rheumatologic disease	AOR 2.12	P 29427797
Liver disease	AOR 1.77	P 29427797
Renal disease	AOR 1.28	P 29427797

These cluster into two mechanistic themes: **barrier breaches** (wounds, ulcers, tinea pedis, excoriating skin disease) and **impaired drainage** (lymphedema, chronic edema, varicose veins, obesity, vein harvest). Additional host risk factors include diabetes mellitus, older age, immunosuppression, and congestive heart failure (an ICU-symposium population study

reported increased cellulitis risk in CHF, PMID: 27885969). An SSTI resource-utilization cohort confirmed diabetes (OR 1.65), chronic kidney disease (OR 1.34), and lymphedema (OR 1.85) as predictors of adverse hospital course (PMID: 42759235).

Genetic risk factors. There are **no established Mendelian causal genes or GWAS-confirmed susceptibility loci** for cellulitis. Host genetic contribution is indirect (e.g., genetic conditions producing lymphedema, immunodeficiency, or diabetes would raise risk). This is a key "not applicable" for this disease.

Protective factors. Modifiable/environmental protective factors are the mirror image of the risk factors: treatment of tinea pedis and interdigital maceration, wound care, weight reduction, and control of chronic edema (compression) all reduce risk. Antibiotic prophylaxis (penicillin) reduces recurrence. No genetic protective variants are established.

Gene–environment interactions. The most relevant "gene–environment" axis is **pathogen genetics × host environment**: e.g., group A *Streptococcus* strains carrying covR/covS regulatory mutations produce more toxin and cause more aggressive local infection (see Section 6), and diabetic (immunocompromised) hosts allow pathogen regulatory pathways (e.g., staphylococcal ClpX-dependent pathways, PMID: 42262120) to exacerbate disease. Human germline gene–environment interaction data are not established for cellulitis.

Section 3 — Phenotypes

Cellulitis phenotypes are **clinical signs/symptoms** rather than laboratory-defined. Core manifestations, with suggested HPO terms:

Phenotype	Type	HPO suggestion	Frequency/notes
Erythema (poorly demarcated, spreading)	Clinical sign	HP:0010783 (Erythema)	Near-universal (defining feature)
Localized skin warmth	Clinical sign	HP:0011121 (Abnormality of skin morphology)	Very common
Edema/swelling of affected area	Clinical sign	HP:0000969 (Edema)	Very common
Pain / tenderness	Symptom	HP:0025280 (Pain)	Very common
Fever	Symptom/sign	HP:0001945 (Fever)	Common in moderate–severe disease
Leukocytosis	Laboratory abnormality	HP:0001974 (Leukocytosis)	Component of ALT-70/LRINEC scoring
Tachycardia	Clinical sign	HP:0001649 (Tachycardia)	Component of ALT-70
Lymphangitis / regional lymphadenopathy	Clinical sign	HP:0002716 (Lymphadenopathy)	Variable
Bullae / skin necrosis	Clinical sign	HP:0008066 (Abnormal blistering of the skin)	Red flag for necrotizing infection

Characteristics. *Age of onset:* any age but incidence rises with age; lower-extremity disease predominates in adults and the elderly. Periorbital cellulitis is disproportionately pediatric. *Severity:* variable, from mild outpatient-managed cellulitis to severe/systemic disease with sepsis. *Progression:* typically acute and progressive over hours to a few days; **episodic/ recurrent** over a patient's lifetime is characteristic in those with chronic edema. *Frequency among affected:* recurrence is common — in prophylaxis-trial control arms, 33–40% of high-risk patients had a recurrence within the study window (PMID: 23635049; PMID: 32786188).

Quality-of-life impact. Cellulitis, especially recurrent disease, imposes significant QOL burden and healthcare cost; chronic edema and repeated episodes cause pain, immobility, missed work, and hospital admissions (PMID: 31420389, ICTOC protocol; PMID: 33238162).

Section 4 — Genetic / Molecular Information

This section is largely "not applicable" in the Mendelian sense. Cellulitis has:

- **No causal human genes**, no OMIM phenotype, no pathogenic germline variants, no ACMG/AMP variant classifications, no modifier genes, no disease-defining chromosomal abnormalities, and no established disease-specific epigenetic signatures.
- **Molecular genetics resides in the pathogen.** The clinically important "genetics" of cellulitis are microbial virulence determinants. In group A *Streptococcus* (GAS), the **covR/covS (CsrRS) two-component regulatory system** controls virulence-gene expression; loss-of-function mutations de-repress toxins and are frequent in severe invasive disease (necrotizing fasciitis, toxic shock). Key toxin genes include *speB* (streptococcal pyrogenic exotoxin B, a cysteine protease) and *sagA*/the *sag* operon encoding **streptolysin S (SLS)** (see Section 6 and **Finding F005**, PMID: 41175456). Additional pathogen-genetics literature reviewed here includes acquisition of toxin-encoding lysogenic bacteriophage elements enhancing GAS virulence (PMID: 41661104), a socially-regulated teichoic-acid-like wall modification associated with immune suppression (PMID: 41733371), and a staphylococcal ClpX-dependent regulatory pathway that exacerbates infection in diabetes (PMID: 42262120).

Suggested gene annotations (pathogen, not human): GAS *covR*/*covS*, *speB*, *sagA*/streptolysin S; *S. aureus* toxin/regulatory loci.

Section 5 — Environmental Information

Environmental/host factors (non-genetic) are the principal drivers (see Section 2): skin barrier disruption (trauma, wounds, ulcers, tinea pedis, eczema, injection drug use), chronic edema/lymphedema, venous insufficiency/varicose veins, obesity, diabetes, prior surgery (e.g., saphenous vein harvest), and immunosuppression.

Lifestyle factors. Obesity is a robust modifiable risk factor (AOR ~2.05). Injection drug use is a recognized portal of entry and outbreak source (e.g., wound botulism among people who inject drugs, PMID: 27885969). Poor foot hygiene facilitating tinea pedis increases risk.

Infectious agents (NCBI Taxonomy).

Organism	NCBI Taxon	Role
Streptococcus pyogenes (group A)	txid1314	Predominant cause of non-purulent cellulitis
β-hemolytic streptococci groups B/C/G (incl. *S. dysgalactiae*)	e.g., *S. agalactiae* txid1311	Common causes, esp. in comorbid hosts
Staphylococcus aureus (incl. MRSA)	txid1280	Purulent cellulitis/abscess
Haemophilus influenzae type b	txid727	Historically periorbital/orbital cellulitis (now rare post-vaccine)
Streptococcus pneumoniae	txid1313	Periorbital/orbital cellulitis
Burkholderia pseudomallei	txid28450	Melioidosis mimicking necrotizing SSTI in endemic areas/diabetics
Vibrio/*Aeromonas* spp.	—	Water-exposure cellulitis

Section 6 — Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. **A skin-barrier breach** (tinea pedis interdigital fissure, wound, ulcer, excoriation, surgical incision) **creates a portal of entry** for bacteria into the deep dermis/subcutis. *(Demonstrated epidemiologically via strong ORs for wounds/ulcers/tinea; F002.)*
2. **Impaired lymphatic/venous drainage** (lymphedema, chronic edema, venous insufficiency, obesity) **results in** local stasis, protein-rich interstitial fluid, and reduced immune surveillance, which **lowers the inoculum threshold** needed to establish infection. *(Inferred mechanistically; supported by strong ORs for lymphedema/edema and by the therapeutic success of compression; F002, F009.)*
3. **Bacteria (predominantly β-hemolytic streptococci) invade and proliferate** in subcutaneous tissue. *(Demonstrated microbiologically; F001.)*
4. **Secreted virulence factors mediate tissue damage.** In GAS, covR/covS regulatory mutations de-repress toxins; **SpeB cleaves gasdermin A → keratinocyte pyroptotic death**, and **streptolysin S (SLS) drives keratinocyte and macrophage death with elevated**

IL-1β, producing larger lesions. *(Demonstrated in mouse subcutaneous infection model; F005: SLS-deficient ΔcovR mutant showed reduced lesion size and mortality.)*

5. **Toxin-mediated cell death and pathogen-associated molecular patterns trigger a brisk innate immune/inflammatory response** — cytokine release (IL-1β, IL-6, TNF), neutrophil recruitment, vasodilation, and increased vascular permeability. *(Inferred from toxin biology and standard inflammation pathways.)*
6. **Inflammation and edema produce the cardinal clinical signs**: erythema, warmth, swelling, pain/tenderness — the diagnosable phenotype. *(Demonstrated clinically.)*
7. **Branch A — resolution:** appropriate antibiotics + host defenses clear infection; inflammation subsides.
8. **Branch B — recurrence loop:** each episode **further damages lymphatics → worsens drainage → predisposes to the next episode** (previous cellulitis is the single strongest risk factor, OR 40.3). *(Demonstrated epidemiologically; interrupted by prophylaxis/compression; F002, F003, F009.)*
9. **Branch C — escalation to necrotizing infection:** with highly virulent strains (covR/covS mutants) or vulnerable hosts, infection **extends to fascia → necrotizing fasciitis**, a surgical emergency with tissue ischemia/necrosis. *(Demonstrated; distinguished by LRINEC score; F011.)*
10. **Branch D — host-factor amplification (diabetes):** neuropathy + peripheral arterial disease + immune impairment **allow progression** from superficial cellulitis to deep abscess, osteomyelitis, gangrene, and amputation. *(Demonstrated clinically; F010.)*

Detail by category

- **Molecular pathways / cellular processes:** Innate inflammatory signaling — pattern-recognition (TLR) activation, inflammasome activation (IL-1β maturation), NF-κB–driven cytokine transcription; **pyroptosis** via gasdermin A (SpeB-cleaved). GO suggestions: GO:0006954 (inflammatory response), GO:0070269 (pyroptosis), GO:0050830 (defense response to Gram-positive bacterium), GO:0032611 (interleukin-1 beta production), GO:0071224 (cellular response to peptidoglycan).
- **Protein dysfunction (pathogen effectors):** SpeB is a secreted cysteine protease (gain of destructive proteolytic function on host gasdermin A); SLS is a post-translationally modified cytolytic peptide.
- **Immune system involvement:** Predominantly **acute innate inflammation** rather than autoimmunity/immunodeficiency (though host immunodeficiency raises susceptibility and severity). IL-1β is a notable mediator (F005).

- **Tissue damage mechanisms:** toxin-mediated cytolysis/pyroptosis (keratinocytes, macrophages), inflammatory edema, and — in the necrotizing branch — ischemia and necrosis.
- **Cell types (CL suggestions):** keratinocyte (CL:0000312), macrophage (CL:0000235), neutrophil (CL:0000775), dermal fibroblast (CL:0002620), lymphatic endothelial cell (CL:0002138).
- **Molecular profiling / advanced technologies:** No human transcriptomic/proteomic/metabolomic disease signatures are established for cellulitis; mechanistic omics evidence derives from pathogen models (mouse subcutaneous infection; covR/covS mutant expression profiling of SLS, F005).

Section 7 — Anatomical Structures Affected

- **Organ level (primary):** skin (UBERON:0002097) — specifically the **deep dermis** (UBERON:0002067) and **subcutaneous tissue / hypodermis** (UBERON:0002072). Erysipelas involves the **upper dermis and superficial lymphatics**.
- **Most common site:** lower extremity/leg (UBERON:0000978) — 88% of lymphedema-related cellulitis admissions were lower-extremity (PMID: 32932222).
- **Site-specific entities:** periorbital/preseptal tissue and orbit (UBERON:0001697 orbit) — periorbital vs. orbital cellulitis (F008); face; diabetic foot/hand (PMID: 19882060).
- **Secondary/complication involvement:** lymphatic vessels (lymphangitis; UBERON:0001473), regional lymph nodes (lymphadenitis), fascia (necrotizing fasciitis; UBERON:0007844), bone (osteomyelitis in diabetic foot), bloodstream (bacteremia/sepsis), and, for orbital cellulitis, the CNS/cavernous sinus (intracranial extension).
- **Tissue types:** connective tissue (subcutis), vascular/lymphatic endothelium, epidermis (keratinocytes at barrier).
- **Subcellular (GO cellular component):** extracellular space (GO:0005615) — site of toxin action; host plasma membrane (GO:0005886) — target of pore-forming SLS/gasdermin pores.
- **Lateralization:** characteristically **unilateral** (asymmetry is a diagnostic clue — the "A" in ALT-70). Bilateral lower-leg erythema more often indicates a mimic (e.g., stasis dermatitis).

Section 8 — Temporal Development

- **Onset: acute**, over hours to a few days. Any age; incidence increases with age and comorbidity. Periorbital cellulitis skews pediatric.
- **Progression:** rapidly progressive erythema is typical; **red-flag rapid spread with systemic toxicity, disproportionate pain, or bullae** signals possible necrotizing infection (F011).
- **Course pattern:** Individual episodes are usually **self-limited with appropriate treatment** (days to ~1–2 weeks). Over a lifetime, disease is frequently **episodic/recurrent** in patients with chronic edema.
- **Duration:** uncomplicated cellulitis treated 5–7 days; complicated/bacteremic disease longer.
- **Remission/critical periods:** Prophylaxis and compression alter the natural history of recurrence — notably, penicillin's protective effect **waned after prophylaxis stopped** (F003), indicating an ongoing-intervention-dependent window. Early recognition of the necrotizing branch is the critical time-sensitive intervention opportunity (early debridement).

Section 9 — Inheritance and Population

- **Inheritance: None** — acquired infectious disease. No inheritance pattern, penetrance, expressivity, anticipation, mosaicism, founder effects, consanguinity, or carrier frequency applies.
- **Epidemiology / burden (Finding F006):** Cellulitis/erysipelas is a frequent primary ED diagnosis. In the US National Emergency Department Sample (2006–2016, ~320 million ED visits), the mean ED-visit cost "*more than doubled in adults (from \$720 to \$1680) and tripled in children (from \$939 to \$2,823)*" (PMID: 33238162). It is associated with public/no insurance, lower income, and weekend/summer presentation; most visits are for uncomplicated disease.
- **Lymphedema link (F006):** In the National Inpatient Sample (2012–2017), of ~165,055 lymphedema-related admissions, "*the vast majority of hospitalizations were for cellulitis (92%), lower extremity disease (88%)*" (PMID: 32932222); inpatient mortality was low (0.03%), with age >80 (OR 3.83) and Charlson comorbidity index ≥3 (OR 4.13) predicting inpatient death.

- **Demographics:** Rises with age; strong comorbidity associations (obesity, diabetes, venous/lymphatic disease). No strong ethnic/founder predisposition (consistent with acquired etiology). Geographic variation is driven by pathogen exposure (e.g., melioidosis in Southeast Asia/northern Australia).

Section 10 — Diagnostics

Cellulitis is a clinical diagnosis — there is no confirmatory gold-standard test. Blood and skin cultures are frequently negative (e.g., usually negative in periorbital/orbital series, PMID: 20544674).

Laboratory / biomarkers: Non-specific inflammatory markers (leukocytosis, elevated CRP) support but do not confirm the diagnosis and feed prediction scores. Blood cultures are low-yield except in systemic illness.

Clinical prediction tools (Finding F004): The **ALT-70 model** (Asymmetry, Leukocytosis, Tachycardia, Age ≥70) "*offers an objective tool to help differentiate between cellulitis and other clinically similar conditions at the time of initial emergency department (ED) presentation*" and retains predictive value at 24 and 48 hours (PMID: 30914341). **Dermatology consultation** frequently modifies management and reduces unnecessary antibiotics/hospitalization (PMID: 39614879).

Differential diagnosis (critical): ~One-third of admitted "cellulitis" is **pseudocellulitis** — "*Inflammatory dermatoses of the lower extremity are often misdiagnosed as cellulitis (aka 'pseudocellulitis') and treated with antibiotics and/or hospitalization*" (PMID: 27806170). Common mimics: stasis dermatitis, contact dermatitis, lipodermatosclerosis, DVT, gout, and infectious mimics (cryptococcosis PMID: 42240944, kerion/tinea PMID: 42670489).

The high-stakes branch — necrotizing fasciitis (Finding F011): NF "*is a rapidly progressing infection of the soft tissues associated with high morbidity and mortality and hence it is a surgical emergency*"; the **LRINEC score ≥6** yielded a C-statistic of 0.839 (95% CI 0.682–0.995, P=0.001) for NF vs. severe cellulitis (PMID: 36462382). Atypical pathogens (melioidosis) can mimic NSTI in endemic areas (PMID: 41580634).

Imaging: Ultrasound helps exclude abscess and DVT; MRI increases sensitivity/specificity for deep involvement (osteomyelitis in diabetic foot, PMID: 27377687; intramuscular abscess in melioidosis, PMID: 41580634); CT for orbital cellulitis and sinusitis.

Genetic/omics diagnostics: Not applicable — no role for genetic testing, karyotyping, CMA, or human omics diagnostics in cellulitis.

Section 11 — Outcome / Prognosis

- **Overall prognosis is good** for uncomplicated disease. Inpatient mortality for lymphedema-related cellulitis was 0.03% (F006).
- **Recurrence** is the dominant morbidity: 33–40% of high-risk patients recur without prophylaxis (F003, F009).
- **Complications:** bacteremia/sepsis, abscess, lymphangitis, recurrent episodes with progressive lymphatic damage, necrotizing fasciitis (surgical emergency, high mortality), and — in orbital cellulitis — vision loss, intracranial extension, and death (F008, PMID: 40642363). In diabetes, progression to osteomyelitis, gangrene, and **amputation** (digit amputation in 14.3% of a diabetic hand-sepsis series, PMID: 19882060).
- **Prognostic factors:** advanced age (>80, OR 3.83 for inpatient mortality), comorbidity burden (Charlson ≥3, OR 4.13), diabetes, chronic kidney disease, lymphedema, and systemic inflammatory response (SIRS OR 4.43 for adverse hospital course, PMID: 42759235). Return ED visits requiring admission in older adults carry higher in-hospital mortality, with cellulitis among the top diagnoses (PMID: 42215907).

Section 12 — Treatment

First-line pharmacotherapy targets streptococci for non-purulent disease (Finding F007). A multicenter double-blind RCT (5 US EDs, N=496) tested cephalexin + trimethoprim-sulfamethoxazole vs. cephalexin + placebo for uncomplicated cellulitis (abscess excluded by ultrasound) and found **no benefit from adding MRSA coverage**: "*For cellulitis without purulent drainage, β-hemolytic streptococci are presumed to be the predominant pathogens. It is unknown if antimicrobial regimens possessing in vitro MRSA activity provide improved outcomes compared with treatments lacking MRSA activity*" (PMID: 28535235). This anchors streptococcal-targeted therapy for uncomplicated non-purulent cellulitis.

Drug / class	Role	NCIT suggestion
Cephalexin (1st-gen cephalosporin)	First-line, non-purulent	NCIT:C349
Dicloxacillin / flucloxacillin (anti-staph penicillin)	First-line	—
Penicillin V/G	Streptococcal cellulitis; prophylaxis	NCIT:C376
TMP-SMX, clindamycin, doxycycline	Add for purulent/MRSA-risk	—
Vancomycin	Severe/IV MRSA coverage	NCIT:C932
Daptomycin	Complicated SSTI (esp. elderly), incl. MRSA	—
Oritavancin, dalbavancin, tedizolid, ceftaroline, delafloxacin, omadacycline	Newer QIDP ABSSSI agents; single-dose options reduce admissions	—

Supporting drug evidence: newer ABSSSI agents reviewed in PMID: 31528278; single-dose oritavancin safety in the SOLO phase 3 trials (PMID: 29358292); daptomycin first-line in elderly complicated SSTI (PMID: 23990341).

Purulent cellulitis / abscess: incision and drainage is central (I&D associated with lower odds of adverse hospital course, OR 0.16, PMID: 42759235), plus MRSA-active antibiotics.

Diabetic foot / severe disease (Finding F010): mild/moderate infection is empirically treated for gram-positive cocci, whereas "*severe or infection caused by drug resistant organisms needs broad spectrum anti-microbial targeting aggressive gram-negative aerobes and obligate anaerobes*," with surgical debridement/amputation as needed (PMID: 27377687; surgical management PMID: 18512303).

Necrotizing fasciitis: early surgical debridement is the definitive intervention alongside broad-spectrum antibiotics (F011).

Orbital cellulitis: IV antibiotics, ENT/ophthalmology involvement, drainage of sinus/orbital abscess when indicated (F008).

Supportive care: limb elevation, analgesia, treatment of the portal of entry (e.g., antifungals for tinea pedis), and edema management.

Pharmacogenomics / advanced (gene/cell/RNA) therapeutics: Not applicable to cellulitis.

Section 13 — Prevention

Primary prevention: treat and prevent barrier breaches (tinea pedis, wounds, eczema), control chronic edema, weight management, glycemic control, and good foot/skin hygiene (targets the risk factors in F002).

Secondary/tertiary prevention — two RCT-backed interventions:

1. **Prophylactic low-dose penicillin V (Finding F003, PATCH I).** In a double-blind RCT of 274 patients with ≥2 leg-cellulitis episodes, penicillin V 250 mg twice daily reduced recurrence: "*During the prophylaxis phase, 30 of 136 participants in the penicillin group (22%) had a recurrence, as compared with 51 of 138 participants in the placebo group (37%) (hazard ratio, 0.55; 95% confidence interval [CI], 0.35 to 0.86; P=0.01), yielding a number needed to treat to prevent one recurrent cellulitis episode of 5*" (PMID: 23635049). PATCH II (underpowered, n=123) was directionally concordant (HR 0.53, P=0.08, PMID: 21910701); pooled economic analysis showed "*a 29% reduction in the number of recurrences... (IRR: 0.71 95%CI: 0.53 to 0.90, p = 0.02)*" (PMID: 24551029). **Caveat:** protective effect waned after stopping prophylaxis.
2. **Compression therapy for chronic leg edema (Finding F009, Webb NEJM).** Single-center RCT (N=84) of compression + education vs. education alone: "*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)*" — trial **stopped early for efficacy** (PMID: 32786188). Extended follow-up confirmed sustained benefit and identified that "*Chronic oedema is a key modifiable risk factor for incident and recurrent cellulitis*" (PMID: 42597865); compression is cost-saving (PMID: 35997601).

Immunization (Finding F008, site-specific). The **Haemophilus influenzae type b (Hib) vaccine** dramatically reduced Hib-related periorbital/orbital cellulitis: "*The introduction of the Hib vaccine coincided with a sharp decline not only in the number of periorbital and orbital cellulitis cases related to H. influenzae, but also in the annual case rate*" (PMID: 10919886); "*H influenzae type b is no longer a significant pathogen in periorbital or orbital cellulitis*" (PMID: 9310918). No vaccine exists for streptococcal/staphylococcal cellulitis generally.

Genetic screening/counseling: Not applicable.

Section 14 — Other Species / Natural Disease

Cellulitis as a bacterial soft-tissue infection occurs naturally across many mammals. A documented veterinary example: in stocker cattle, **interdigital necrobacillosis (foot rot)** is a polymicrobial interdigital infection where "*breach of skin allows bacteria to cause cellulitis, septic arthritis, and lameness*," implicating *Fusobacterium necrophorum*, with prevention via hygiene and possible *F. necrophorum* vaccination (PMID: 42309844). This mirrors the human "barrier-breach → cellulitis" mechanism.

- **Taxonomy of affected species:** broad — cattle (*Bos taurus*, txid9913), and companion animals (dogs *Canis lupus familiaris* txid9615, cats *Felis catus* txid9685) develop bacterial cellulitis/abscesses from bites and wounds.
- **Comparative biology:** the core mechanism (skin breach + bacterial invasion + inflammation) is evolutionarily conserved; pathogen species differ (e.g., *Fusobacterium* in bovine foot rot).
- **Zoonotic/transmission:** cellulitis itself is not person-to-person transmissible; zoonotic relevance is via animal-bite inoculation (e.g., *Pasteurella*) and shared environmental pathogens.

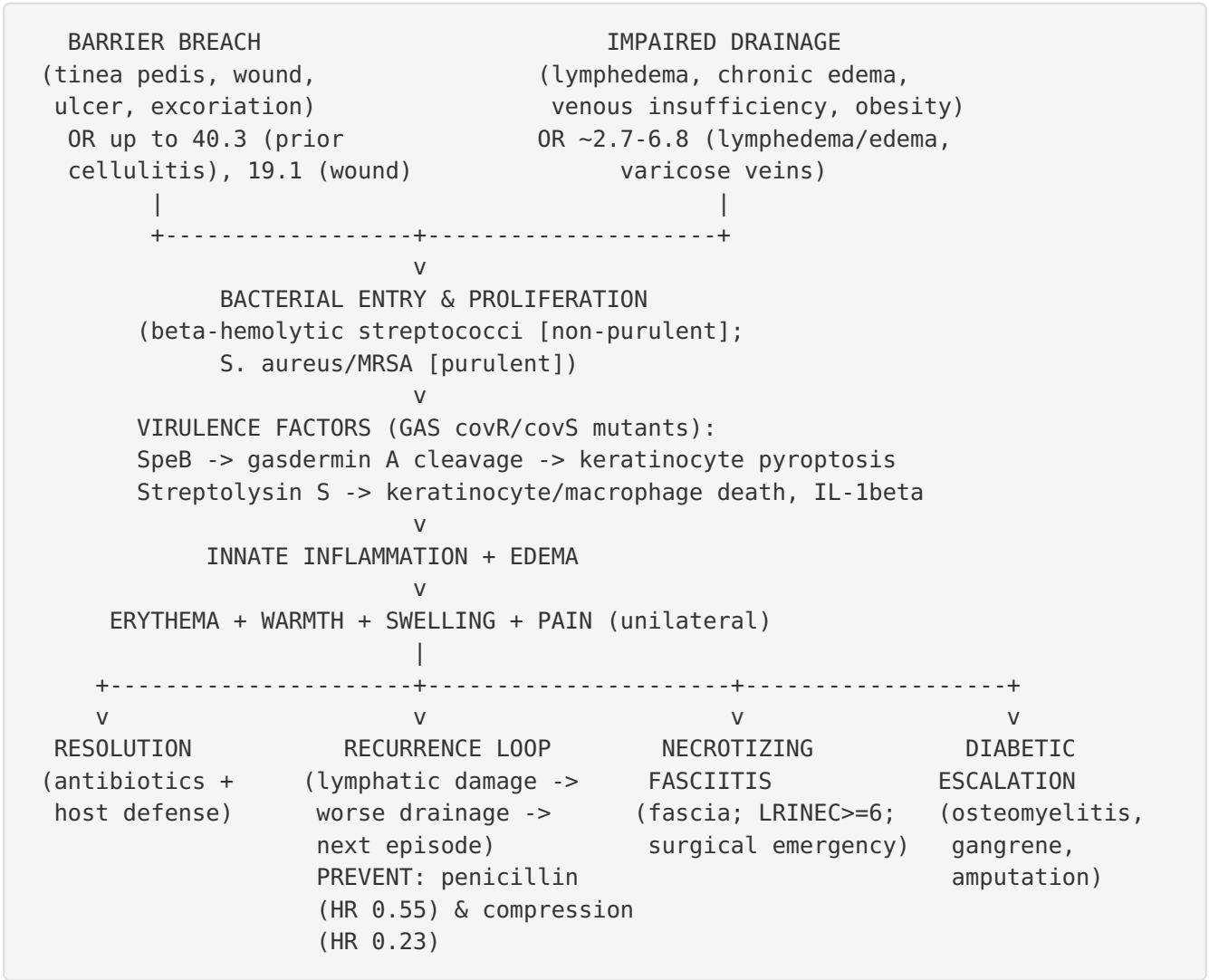
Orthologous "disease genes" are not applicable (no human causal genes). Model-organism pathogen genes (murine GAS infection) are covered in Section 15.

Section 15 — Model Organisms

- **Mouse subcutaneous infection model (primary mechanistic system; Finding F005).** In this model, GAS with covR/covS mutations cause severe local skin lesions; "*SpeB-mediated gasdermin A cleavage triggers keratinocyte death, resulting in sizeable lesion size but preventing invasive skin infection by GAS*," and streptolysin S drives keratinocyte/macrophage death and IL-1β. Causality was demonstrated by loss-of-function: "*In a mouse subcutaneous infection model, the SLS-deficient Δ*covR *mutant exhibited reduced lesion size and mortality compared to the Δ*covR *mutant*" (PMID: 41175456). Model type: mammalian (*Mus musculus*, txid10090), induced by bacterial inoculation, using bacterial genetic knockouts (Δ*covR*, SLS-deficient).
- **Diabetic infection models** support the host-factor branch, e.g., staphylococcal ClpX-dependent regulatory pathways exacerbating infection in diabetes (PMID: 42262120).

- **Phenotype recapitulation:** murine subcutaneous models reproduce local lesion formation, toxin-driven cell death, and virulence-regulator effects well, enabling dissection of pathogen mechanisms.
- **Limitations:** these are **pathogen-mechanism models**, not models of the human host-susceptibility phenotype (chronic edema, lymphedema, recurrence). The two dominant clinical drivers — impaired drainage and recurrence — are not fully captured by acute murine inoculation models. Human disease is not driven by host genetics, so there are no "disease-gene knockout" mouse models of cellulitis per se.

Mechanistic Model / Interpretation



The unifying insight is that cellulitis is a **"two-hit" disease**: neither a barrier breach nor impaired drainage alone reliably causes it, but together they establish infection. This explains why the most effective preventive strategies target the *host substrate* (compression for edema) and *bacterial persistence/recolonization* (penicillin prophylaxis) rather than any intrinsic host genetics. It also explains the self-perpetuating recurrence loop (prior cellulitis = strongest risk factor) via cumulative lymphatic injury.

Evidence Base

PMID	Title (abbrev.)	Supports
42711142	*Non-Purulent Cellulitis—An Updated Review*	F001 microbiology
42727947	*Advances in diagnosis/management of SSTI*	F001 purulent vs non-purulent
27864837	*Risk factors for nonpurulent leg cellulitis (meta-analysis)*	F002 risk factors
29427797	*Severe lower limb cellulitis case-control*	F002 risk factors
23635049	*Penicillin to prevent recurrent leg cellulitis (PATCH I)*	F003 prophylaxis
24551029	*PATCH I&II economic analysis*	F003 pooled effect
21910701	*PATCH II trial*	F003 corroboration
39614879	*Dermatology consultation/diagnostic stewardship*	F004 diagnosis
30914341	*ALT-70 model at 24/48h*	F004 prediction tool
27806170	*Costs of misdiagnosed cellulitis (pseudocellulitis)*	F004 mimics
41175456	*Streptolysin S / covR-covS keratinocyte death*	F005 mechanism
33238162	*Burden of cellulitis/erysipelas in US ED*	F006 burden
32932222	*Epidemiology of lymphedema admissions*	F006 lymphedema link
28535235	*Cephalexin ± TMP-SMX RCT*	F007 treatment
20544674	*Periorbital/orbital cellulitis 10-yr review*	F008 site-specific
10919886	*Pre/post Hib vaccination cellulitis*	F008 vaccine prevention
9310918	*Periorbital/orbital cellulitis in Hib vaccine era*	F008 corroboration
32786188	*Compression therapy RCT (NEJM)*	F009 prevention
42597865	*Sustained benefit of compression (follow-up)*	F009 durability
35997601	*Compression is cost-saving*	F009 economics
27377687	*Understanding diabetic foot infection*	F010 diabetic branch
19882060	*Hand sepsis in diabetes*	F010 amputation risk

PMID	Title (abbrev.)	Supports
36462382	*LRINEC/SIARI validation for NF*	F011 diagnosis branch
41580634	*Melioidosis mimicking NSTI*	F011 mimics
31528278	*New ABSSSI drugs*	Treatment options
29358292	*Oritavancin SOLO safety*	Single-dose therapy
23990341	*Daptomycin in elderly cSSTI*	Treatment (elderly)
42759235	*ED disposition/resource use for SSTI*	Prognostic factors
42309844	*Non-respiratory diseases of stocker cattle*	Veterinary/comparative

Limitations and Knowledge Gaps

1. **Microbiology is largely inferential.** Because cultures are frequently negative in non-purulent cellulitis, the streptococcal predominance is "presumed" from serology, syndromic association, and treatment-response data rather than direct isolation in most patients.
2. **Mechanistic depth comes from pathogen models, not human tissue.** The SpeB/gasdermin A and streptolysin S mechanisms (F005) derive from mouse subcutaneous infection with hypervirulent covR/covS mutants — informative for severe/necrotizing GAS disease but not necessarily representative of ordinary streptococcal cellulitis. No human transcriptomic/proteomic/metabolomic disease signature was identified.
3. **Prevention evidence has scale limits.** The compression RCT (F009) is single-center (N=84, stopped early — early-stopped trials can overestimate effect); PATCH II was underpowered. Penicillin's benefit does not persist after stopping.
4. **Recurrence biology is under-characterized.** The lymphatic-damage recurrence loop is well-supported epidemiologically (prior cellulitis OR 40.3) but the molecular mechanism of episode-induced lymphatic injury is inferred, not directly demonstrated in humans.
5. **No genetic/omics dimension.** Sections on causal genes, variants, inheritance, genetic testing, and pharmacogenomics are genuinely not applicable, consistent with an acquired infection.
6. **Heterogeneous case definitions.** "Cellulitis/erysipelas" grouping and variable coding across administrative datasets limit precision of burden and outcome estimates.

Proposed Follow-up Experiments / Actions

1. **Implement and audit ALT-70 (± LRINEC) at ED triage** to reduce pseudocellulitis over-treatment and to systematically flag necrotizing infection; measure impact on antibiotic days and admissions (F004, F011).
2. **Pragmatic multicenter RCT of combined compression + penicillin prophylaxis** vs. each alone in recurrent leg cellulitis with chronic edema, powered for time-to-recurrence and cost — the two proven interventions have never been directly compared or combined at scale (F003, F009).
3. **Trial of continued vs. tapered penicillin prophylaxis** to address the waning-benefit problem (define optimal duration and identify who can safely stop).
4. **Human mechanistic study of lymphatic function across cellulitis episodes** (e.g., lymphoscintigraphy before/after an episode) to test the hypothesized episode-induced lymphatic-damage recurrence loop.
5. **Skin/blood molecular profiling (transcriptomics, host biomarkers)** in culture-negative non-purulent cellulitis vs. pseudocellulitis to develop an objective diagnostic biomarker.
6. **Structured tinea pedis / interdigital-barrier eradication program** in high-risk (edema/diabetic) patients as a primary-prevention intervention, with cellulitis incidence as the endpoint (targets the barrier-breach hit; F002).
7. **Diabetic foot pathway optimization** integrating early MRI and multidisciplinary surgical review to reduce progression from cellulitis to amputation (F010).

Report generated from a 5-iteration autonomous discovery investigation: 11 confirmed findings, 52 papers reviewed. Evidence types span human clinical RCTs and observational studies (F001–F004, F006–F011) and mouse/in-vitro pathogen-mechanism studies (F005).
