Febrile Ulceronecrotic Mucha–Habermann Disease (FUMHD): A Comprehensive Disease Characteristics Report

Evidence base: aggregated disease-level literature — case reports, case series, and systematic reviews (no dedicated registry/EHR cohort, no omics datasets, no animal models). Evidence type throughout is human clinical unless otherwise noted. 15 findings confirmed across 5 iterations; 41 papers reviewed.

Summary

Febrile Ulceronecrotic Mucha–Habermann Disease (FUMHD) is a rare, fulminant, potentially fatal variant of pityriasis lichenoides et varioliformis acuta (PLEVA) — the acute pole of the pityriasis lichenoides (PL) spectrum (PLC → PLEVA → FUMHD). It is defined by the **sudden onset of generalized, painful, coalescing ulceronecrotic papules and plaques** with hemorrhagic bullae and necrotic crusts, accompanied by **high fever (≥39 °C)** and multi-organ systemic involvement. It frequently begins as classic PLEVA and evolves over days to a few weeks; in adults it may involve more than 90% of the body surface area.

FUMHD is **immune-mediated and non-genetic**. The best-supported model is a **dysregulated cytotoxic CD8⁺ T-cell response**, typically triggered by an infectious/antigenic stimulus (EBV, HSV-2, *Toxoplasma gondii*, HIV, *Mycoplasma*) or hypersensitivity, producing interface dermatitis, keratinocyte necrosis, and lymphocytic vasculitis. Progression to fulminant disease is associated with **markedly elevated serum TNF-α**, which amplifies keratinocyte apoptosis. A subset of cases harbors a **somatic monoclonal T-cell receptor (TCR) rearrangement**, placing FUMHD on a continuum with cutaneous T-cell lymphoma (CTCL) and predicting worse outcomes. Skin-barrier failure leads to superinfection/sepsis, DIC, and multi-organ failure — the dominant causes of death.

Only ~120 cases exist in the world literature. **Case-fatality is ~12–20%, strongly age-dependent (children ~2% vs. adults ~20%)**. Diagnosis is **clinicopathologic** (no universally accepted criteria; Nofal 2016 proposed a constant + variable criteria framework). Treatment is **empirical and multimodal** — systemic corticosteroids, methotrexate, IVIG, antibiotics, and TNF-α inhibitors in refractory cases — balanced against infection risk. There are no causal genes, no animal models, and no applicable primary prevention; efforts focus on early recognition and sepsis prevention.

Key Findings

Finding 1 — Definition and nosology

FUMHD is consistently defined as a rare, severe, potentially fatal PLEVA variant marked by sudden generalized ulceronecrotic papules coalescing into ulcers with high fever and systemic symptoms, often progressing from classic PLEVA. *"Febrile ulceronecrotic Mucha-Habermann disease is a rare and severe variant of pityriasis lichenoides, characterized by sudden onset of generalized ulceronecrotic papules that rapidly coalesce into ulcers associated with high fever"* (PMID: 38959922). The PLEVA-to-FUMHD progression and high mortality are captured by: *"FUMHD often starts out as classic PLEVA, but goes on to develop widespread ulceronecrotic lesions and is associated with a high mortality rate"* (PMID: 15583604).

Finding 2 — Identifiers, synonyms, classification

Because FUMHD is non-Mendelian, no distinct OMIM number exists; identifiers are inherited from the parent PLEVA/PL entity.

Resource	Identifier
MeSH	**Pityriasis Lichenoides** (D017517) — no dedicated FUMHD heading
ICD-10	**L41.0** (Pityriasis lichenoides et varioliformis acuta)
ICD-11	**EA06.0** (Pityriasis lichenoides)
MONDO	**MONDO:0006559** (pityriasis lichenoides et varioliformis acuta)
Orphanet	Under PLEVA
OMIM	None (non-genetic)

Synonyms: FUMHD; ulceronecrotic Mucha–Habermann disease; pityriasis lichenoides et varioliformis acuta fulminans; PLEVA fulminans; (historic) acute parapsoriasis. Information derives from aggregated disease-level resources and pooled case reports, **not** individual-patient EHR data.

Finding 3 — Epidemiology

FUMHD is extremely rare. A systematic MEDLINE review identified **119 cases** with overall lethality 14/119 (**12%**, CI 6–17%), children 2% (1/54) vs. adults 20% (13/65): *"Literature review revealed 119 FUMHD cases. Overall lethality was 14/119 (12%, CI 6-17%), and lethality in children was lower (1/54, 2%, CI 0-6%) compared to adults (13/65, 20%, CI 11-31%)"* (PMID: 34287852). An independent PRISMA review found 68 patients across 63 publications: *"Out of 68 patients, 55 patients had their condition fully resolved and 13 cases were fatal"* (PMID: 36483219). No formal prevalence/incidence estimates exist. There is a clear **male predominance (~75%)** across all ages.

Finding 4 — Clinical phenotype

The core cutaneous phenotype is sudden, generalized, painful, coalescing ulceronecrotic papules/plaques with hemorrhagic bullae and necrotic crusts, healing with varioliform scars and dyspigmentation; constitutional features include high fever, malaise, arthralgia, and lymphadenopathy. Quantitatively: *"Most of them were male (62/83, 74.7%), with high fever state (50/80, 62.5% had a high fever of 39°C or above), and with more positive skin bacterial cultures (31/41, 75.6%)"* (PMID: 35950146).

Suggested HPO terms: Skin ulcer (HP:0200041), Cutaneous/epidermal necrosis (HP:0100683), Papule (HP:0200034), Bulla/vesicle (HP:0008064), Fever (HP:0001945), Arthralgia (HP:0002829), Lymphadenopathy (HP:0002716), Thrombocytopenia (HP:0001873), Abnormal skin pigmentation (HP:0001000), Scarring (HP:0200042). Quality-of-life impact is high during the acute phase (severe pain, extensive open wounds, hospitalization); no formal EQ-5D/SF-36/PROMIS data exist.

Finding 5 — Systemic organ involvement

Systemic manifestations are common and drive mortality: *"Systemic manifestations such as intravascular disseminated coagulation and pulmonary, cardiac, gastrointestinal, and central nervous system involvement are common"* (PMID: 38959922). Complications include DIC, interstitial pneumonitis/ARDS (fatal in one de novo case, PMID: 36686043), cardiac/GI/CNS involvement, cytopenias, and **hemophagocytic lymphohistiocytosis (HLH)**: *"The patient also met 7 of 9 HLH-2004 criteria, leading to a diagnosis of HLH"* (PMID: 38457671). FUMHD can mimic Stevens–Johnson syndrome/TEN and Kawasaki disease (PMID: 31814284).

Finding 6 — Pathogenesis: cytotoxic T cells + TNF-α + clonality

Histology shows a dense perivascular/intramural **$CD8^+$ cytotoxic** lymphocytic infiltrate with interface dermatitis, keratinocyte necrosis, and lymphocytic vasculitis; an atypical immunophenotype is described: *"Biopsy indicated a dermal and subcutaneous infiltrate of atypical CD8+ lymphocytes with loss of CD5 and reduction in CD7 expression, along with features of lymphomatoid vasculitis"* (PMID: 38457671). The PLEVA→FUMHD transition is associated with elevated TNF-α despite normal CRP: *"his skin lesions started to ulcerate progressively, involving > 90% of his body surface, accompanied by high fever, normal C-reactive protein, but highly elevated serum levels of tumour necrosis factor (TNF)-alpha"* (PMID: 15840118). A subset shows monoclonal T cells: *"we report two cases of FUMHD with monoclonal T-cell population, as detected by Southern blot analysis. We propose that clonal FUMHD represents a cutaneous T-cell lymphoma entity"* (PMID: 15583604).

Suggested GO terms: T cell mediated cytotoxicity (GO:0001913), apoptotic process (GO:0006915), inflammatory response (GO:0006954), tumor necrosis factor-mediated signaling (GO:0033209), leukocyte migration (GO:0050900). **Suggested CL terms:** CD8-positive, alpha-beta T cell (CL:0000625); keratinocyte (CL:0000312); vascular endothelial cell.

Finding 7 — Etiology and triggers

Etiology is unknown; three hypotheses dominate: *"PLEVA is speculated to be an inflammatory reaction triggered by certain infectious agents, an inflammatory response secondary to T-cell dyscrasia, or an immune complex-mediated hypersensitivity"* (PMID: 20465660). Infectious triggers of the PL spectrum: *"Epstein-Barr virus, Toxoplasma gondii, and HIV are the most frequently reported infectious triggers of pityriasis lichenoides"* (PMID: 12894107). FUMHD-specific associations include **HSV-2** (PMID: 19103367) and *Mycoplasma*. Preceding infection is documented in 60.3% of pediatric PL with winter/spring seasonality. **No genetic, toxin, lifestyle, or occupational risk factor, and no protective factors or gene–environment interactions** are defined.

Finding 8 — Mortality risk factors and prognosis

"Risk factors for a fatal outcome (likelihood ratio; P) were sepsis (24.97, $P < 0.001$), adult vs. pediatric patient age (11.19; $P = 0.001$), systemic involvement (19.97, $P < 0.001$), and mucosal involvement (4.58; $P = 0.032$)" (PMID: 34287852). A proposed mortality score (Age/10 + 4 + 4·[systemic] + 1·[mucosal]) has 93% sensitivity / 77% specificity, and infection is the leading cause of death: *"infectious complications are a frequent cause of death."* An independent review adds clonality: *"Increased age, systemic involvement, and monoclonal T-cell receptor rearrangement were associated with worst prognosis, but mucosal involvement did not affect mortality risk"* (PMID: 36483219). The adult effect is large: *"Adults were associated with a higher risk of death (OR = 12.976, 95% CI: 1.049, 160.504)"* (PMID: 35950146).

Finding 9 — Diagnosis

Diagnosis is clinicopathologic with exclusion of mimics. Nofal et al. proposed a two-tier framework: *"We propose two sets of diagnostic criteria... The first comprises constant clinical and histopathological features that are always present in every case, the combination of which is necessary for diagnosis. The second set includes variable features that may be present in some cases"* (PMID: 26695875). Characteristic histology/IHC: *"histopathology, which revealed interface dermatitis, intraepidermal vesiculation, and erythrocyte extravasation. Immunohistochemistry revealed perivascular T-cell infiltration"* (PMID: 40560064). Supportive labs: leukocytosis/leukopenia, thrombocytopenia, elevated inflammatory markers, elevated serum TNF-α, frequent positive cultures, plus a **TCR clonality assay** for prognosis. **Genetic/newborn/carrier testing is not applicable.** Differential diagnosis: PLEVA, lymphomatoid papulosis, CTCL, SJS/TEN, erythema multiforme, Kawasaki disease, varicella, vasculitis, ecthyma.

Finding 10 — Treatment

No RCTs exist; therapy is empirical and multimodal: *"Successful treatment modalities for FUMHD included antibiotics, antivirals, systemic steroids, Methotrexate (MTX), cyclophosphamide, Cyclosporine (CYA), Intravenous Immunoglobulins (IVIG), pentoxifylline, and ultraviolet B phototherapy"* (PMID: 36483219). Methotrexate + antibiotics produced rapid improvement (PMID: 26584702); IVIG can control refractory disease as a single infusion — *"who improved rapidly and achieved disease control with just a single infusion of low-dose intravenous immunoglobulin"* (PMID: 38234081). Consistent with the TNF-α mechanism, TNF-α inhibitors help refractory cases — *"TNFα inhibitors may be useful, particularly in resistant cases"* (PMID: 23391565) — with complete resolution reported (PMID: 26790133); however an infant treated with a TNF-α inhibitor still died (PMID: 42178566). Anti-CD25 basiliximab helped a FUMHD-like eruption with clonal T-ALL (PMID: 28884915). Aggressive wound care and infection control are outcome-determining, and immunosuppression must be *"balanced against the mortality risk, as infectious complications are a frequent cause of death"* (PMID: 34287852).

Suggested MAXO terms: glucocorticoid therapy, methotrexate/antimetabolite therapy, immunoglobulin therapy (IVIG), antimicrobial therapy, TNF inhibitor/biologic therapy, phototherapy (UVB), wound care.

Finding 11 — Temporal development

Onset is acute/subacute across all ages (youngest reported 15 months — *"This report presents the youngest known pediatric case of fatal FUMHD"*, PMID: 42178566 — through adults and pregnancy). It often evolves from classic PLEVA within ~1–3 weeks: *"Three weeks later, his skin lesions started to ulcerate progressively, involving > 90% of his body surface, accompanied by high fever"* (PMID: 15840118). The course is rapidly progressive and potentially fatal untreated, but most patients (especially children) resolve over weeks–months with treatment, healing with varioliform scars; a minority relapse or evolve toward lymphoproliferative disease. **No inheritance pattern** — sporadic and non-familial.

Finding 12 — Genetics, model organisms, and other species (not applicable)

There are **no causal genes, pathogenic germline variants, chromosomal abnormalities, GWAS loci, or heritable susceptibility alleles** for FUMHD. The only molecular abnormality of significance is a **somatically acquired clonal TCR rearrangement** in skin-infiltrating lymphocytes of a subset. **No animal model** (knockout/transgenic/induced) recapitulates FUMHD, and **no naturally occurring animal equivalent** exists (no OMIA entry) — it is a

human-only (NCBITaxon:9606) disease. The nearest in-vivo correlate is FUMHD-like ulceronecrotic disease arising with clonal T-ALL cells (PMID: 28884915) — an observation, not a model. Epigenetic, omics, veterinary, and orthologous-gene sections are **not applicable**.

Finding 13 — Prognosis synthesis

Case-fatality ~12–20% is strongly age-dependent (children ~2% vs. adults ~20%), with the leading cause of death being sepsis of denuded skin and multi-organ failure (DIC, ARDS, CNS). Prognostic factors: adult age, sepsis, systemic involvement, monoclonal TCR. Survivors heal with varioliform scars and dyspigmentation; a subset relapse or progress toward CTCL. No formal 5-/10-year survival statistics exist (rare disease).

Finding 14 — Prevention

Because FUMHD is sporadic, non-genetic, and of unknown etiology with no modifiable exposure, **no primary prevention** applies. Prevention is secondary (early recognition + prompt therapy) and tertiary (prevent superinfection/sepsis via wound care, barrier protection, surveillance cultures, timely antimicrobials): management centers on *"prevention and care of skin injuries and complications"* (PMID: 38715678). Immunization, public-health/environmental interventions, and genetic counseling are not relevant.

Finding 15 — Integrated synthesis

Integrating all findings yields a coherent staged model (below): an infectious/antigenic or hypersensitivity trigger initiates a dysregulated cytotoxic $CD8^+$ T-cell response; elevated TNF-α amplifies keratinocyte apoptosis, driving PLEVA→FUMHD; a subset acquires monoclonal TCR clonality (CTCL continuum, worse prognosis); and skin-barrier failure produces the lethal sepsis/multi-organ node. This explains why TNF-α blockade and immunomodulation work while infection control is simultaneously critical (PMID: 15840118; PMID: 36483219).

Mechanistic Model / Interpretation

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  [Trigger]                [Immune dysregulation]            [Amplification]            [Sy
Infection / antigen  →   Dysregulated cytotoxic CD8+   →   Elevated serum TNF-α    →   Skin-bar
(EBV, HSV-2,             T-cell response:                  amplifies keratinocyte    superinfe
Toxoplasma, HIV,         interface dermatitis,             apoptosis; drives         DIC, pulm
Mycoplasma) OR           keratinocyte necrosis,            PLEVA → FUMHD             CNS, HLH,
hypersensitivity         lymphocytic vasculitis            transition                failure
                                  │
                                  └── subset: somatic monoclonal TCR rearrangement
                                       → continuum with cutaneous T-cell lymphoma (CTCL)
                                       → worse prognosis
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Upstream vs. downstream. The trigger and cytotoxic CD8⁺ T-cell response are **upstream**. TNF-α–driven keratinocyte apoptosis is the **key amplifier** converting limited PLEVA into confluent ulceronecrosis. The **downstream, lethal** events are barrier failure → sepsis, DIC, and multi-organ dysfunction. The clonal-TCR arm is a parallel modifier shifting a subset toward a lymphoproliferative phenotype and worse outcomes. This dual structure explains the therapeutic tension: immunosuppression targets the upstream/amplification nodes while antibiotics and wound care address the downstream node — and over-immunosuppression heightens the very sepsis risk that most often kills.

Model node	Evidence	Key PMIDs
Infectious/antigenic trigger	EBV/Toxoplasma/HIV; HSV-2; *Mycoplasma*; 60.3% preceding infection in pediatric PL	12894107, 19103367, 20465660
Cytotoxic CD8⁺ T-cell / vasculitis	Atypical CD8⁺ infiltrate, interface dermatitis, lymphomatoid vasculitis	38457671, 40560064
TNF-α amplification	Elevated serum TNF-α at PLEVA→FUMHD transition; normal CRP	15840118
Clonal TCR / CTCL continuum	Monoclonal T-cell population; worse prognosis	15583604, 36483219
Sepsis / multi-organ failure	Sepsis LR 24.97; DIC/pulmonary/cardiac/GI/CNS; HLH	34287852, 38959922, 38457671

Anatomical involvement (ontology mapping)

- **Primary organ:** skin (UBERON:0002097) — epidermis (UBERON:0001003), dermis (UBERON:0002067); epithelial + connective tissue with superficial dermal vasculitis.
- **Secondary/multi-organ:** lung (UBERON:0002048), heart (UBERON:0000948), GI tract (UBERON:0000160), brain/CNS (UBERON:0000955), blood/coagulation system, reticuloendothelial/immune system (HLH); mucous membranes may be involved.
- **Cells:** keratinocytes (CL:0000312, target of necrosis), $CD8^+$ cytotoxic T lymphocytes (CL:0000625), dermal microvascular endothelium.
- **Localization/lateralization:** generalized, bilateral and symmetric; trunk and flexural extremities predominate, often facial/acral.

Evidence Base

PMID	Title (abbreviated)	Contribution
34287852	Mucha-Habermann disease: pediatric case + risk score	Largest review (119 cases); mortality, LR risk factors, risk score
36483219	Mortality risk factors: systematic review	68-patient review; treatment modalities; clonal-TCR prognosis
35950146	Case report + systematic review	Phenotype frequencies (sex, fever, cultures); adult death OR
38959922	Case + treatment review	Core definition; systemic organ involvement
15583604	FUMHD with clonality: a CTCL entity?	Monoclonal T cells; CTCL continuum
15840118	PLEVA→FUMHD transition + TNF-α	TNF-α as pathogenic driver
38457671	FUMHD with HLH	$CD8^+$ immunophenotype; HLH complication
26695875	Proposed diagnostic criteria	Constant vs. variable criteria framework
40560064	22-month-old case	Histopathologic/IHC diagnostic features
20465660	PLEVA disease spectrum	Three etiologic hypotheses
12894107	Infectious causes of PL	Principal infectious triggers
19103367	FUMHD with HSV-2	HSV-2 trigger; clonality as prognostic marker
23391565	Infliximab + IVIG	First TNF-α inhibitor use in FUMHD
38234081	IVIG in a child	IVIG efficacy in refractory pediatric FUMHD
26584702	Two cases responsive to MTX	Methotrexate + antibiotics efficacy
28884915	FUMHD-like disease in T-ALL	Basiliximab; clonal-leukemia link
36686043	De novo FUMHD, fatal pulmonary	Fatal ARDS; no established criteria
42178566	Fatal pediatric case	Youngest fatal case; TNF-inhibitor failure
38715678	Case report	Prevention/care of skin injuries
31814284	FUMHD mimicking Kawasaki	Differential diagnosis

Supporting/contextual literature includes pediatric PL cohorts confirming male predominance, seasonality, and non-progression of childhood PL to mycosis fungoides (PMID: 42152620, PMID: 41420620), and a review positioning FUMHD as a complication of the acute PL form (PMID: 27144956).

A note of tension: The two large systematic reviews disagree on whether **mucosal involvement** independently affects mortality — significant in Blohm et al. (PMID: 34287852; LR 4.58, P=0.032) but not in Tasouli-Drakou et al. (PMID: 36483219). This should be interpreted cautiously given small numbers and heterogeneous reporting.

Supported vs. Refuted Hypotheses

Supported: - FUMHD is a fulminant, potentially fatal PLEVA variant (multiple reviews). - Pathogenesis is cytotoxic-T-cell–mediated with elevated TNF-α; a subset is clonal/CTCL-like. - Mortality is age-dependent and driven by sepsis and systemic involvement. - Multimodal immunosuppression + infection control is the mainstay; TNF-α inhibitors help refractory cases.

Refuted / Not applicable: - A Mendelian/genetic cause (no causal gene; no OMIM). - Existence of animal models or natural animal disease. - Availability of omics datasets, formal incidence/prevalence, or RCT-grade treatment evidence. - A consistent effect of mucosal involvement on mortality (contradictory between reviews).

Limitations and Knowledge Gaps

1. **Evidence quality.** The literature is composed entirely of case reports and case-series-based systematic reviews — substantial publication/selection bias (severe and fatal cases and treatment "successes" preferentially reported), heterogeneous reporting, and short follow-up.
2. **Unknown etiology.** The precise trigger and the host factors determining why only rare individuals progress from PLEVA to FUMHD remain undefined.
3. **Mechanistic depth.** The TNF-α / cytotoxic $CD8^+$ model rests on limited biomarker and IHC data; no transcriptomic, proteomic, single-cell, or spatial profiling of FUMHD lesions exists, and TNF-α causality is inferred.

4. **Clonality significance.** Whether monoclonal TCR marks a distinct CTCL subset or a transient reactive clone is unresolved; TCR-PCR data exist for only a handful of cases.
5. **No animal model** precludes controlled mechanistic and therapeutic experimentation.
6. **Diagnostic heterogeneity.** Absence of universally adopted criteria affects case ascertainment and reported frequencies/mortality.
7. **Ontology IDs** (MONDO/ICD/MeSH) should be verified against current releases.

Proposed Follow-up Experiments / Actions

1. **Establish an international FUMHD registry** with standardized capture (Nofal criteria, systemic involvement, cultures, TCR clonality, treatments, long-term outcomes) to move beyond isolated case reports and prospectively validate the Blohm mortality risk score.
2. **Longitudinal biomarker profiling** of serum and lesional tissue (TNF-α, IL-2, IFN-γ) across the PLEVA→FUMHD transition to test the TNF-α amplification hypothesis and find progression-predictive markers.
3. **Single-cell and spatial transcriptomics** of lesional skin to characterize the cytotoxic infiltrate, clonal architecture, and keratinocyte/endothelial injury programs, distinguishing reactive from neoplastic clones.
4. **Systematic high-throughput TCR clonality analysis** across a case series to quantify prevalence and prognostic weight of monoclonality and its relationship to CTCL evolution.
5. **Structured infectious-trigger workup** (EBV, HSV-2, *Toxoplasma*, HIV, *Mycoplasma*) applied uniformly at presentation to quantify trigger frequency.
6. **Individual-patient-data meta-analysis** of treatment outcomes to estimate the relative effect of TNF-α inhibitors, IVIG, methotrexate, and corticosteroids while adjusting for severity and the competing risk of sepsis.
7. **Consensus diagnostic-criteria adoption** — validate and operationalize the Nofal framework across centers to harmonize case ascertainment.

Report compiled from 15 confirmed findings across 5 investigation iterations and 41 reviewed papers. Evidence source type: predominantly human clinical (case reports and case-series systematic reviews); no model-organism, in-vitro, or computational primary data exist for this disease.
