Acute Cystitis (MONDO:0001650): A Comprehensive Disease Characteristics Report

Autonomous discovery investigation — 5 iterations, 21 confirmed findings, 69 papers reviewed

Summary

Acute cystitis is an acute bacterial infection of the urinary bladder, caused predominantly by uropathogenic *Escherichia coli* (UPEC, ~75–90% of cases), which adheres to the bladder urothelium via the FimH type-1-pilus adhesin, invades superficial umbrella cells, forms intracellular bacterial communities (IBCs), and triggers a TLR4–NF-κB innate-immune response that produces the classic dysuria–frequency–urgency syndrome. It is one of the most common human bacterial infections, with a striking female predominance: 50–60% of adult women experience at least one episode in their lifetime. Etiology is infectious and multifactorial/polygenic (not Mendelian); host genetic modifiers such as *TLR2*, *CXCR1*, and *FUT2* (secretor status) modulate susceptibility, and behavioral factors (sexual intercourse, spermicide use, prior UTI, diabetes) are dominant risk drivers.

Diagnosis is primarily clinical, supported by urine dipstick (leukocyte esterase and nitrite) and, when indicated, urine culture. Guideline-endorsed first-line therapy comprises **nitrofurantoin, trimethoprim–sulfamethoxazole (TMP-SMX), fosfomycin, and pivmecillinam**; fluoroquinolones are explicitly de-prioritized because of FDA black-box safety warnings and rising resistance. Prognosis is excellent and frequently self-limiting, but recurrence is common (annual recurrence 14–25% in women), and the principal complication is ascending infection to acute pyelonephritis — of particular concern in pregnancy, where it is associated with preterm delivery and low birth weight.

This report synthesizes 21 confirmed findings into a mechanistic causal chain running from FimH-mediated adhesion through urothelial invasion, IBC formation, and TLR4–NF-κB inflammation to clinical symptoms, and covers all 15 requested disease-characteristic domains with ontology-term suggestions (HPO, GO, CL, UBERON, CHEBI, NCIT) and PMID-anchored

evidence. The overall picture is of a well-understood, treatable infectious disease whose principal unsolved problems are recurrence, intracellular bacterial persistence, and antimicrobial resistance — the targets of an emerging class of anti-adhesion (FimH-antagonist / mannoside) and immunoactive (MV140, OM-89) therapeutics.

Section 1 — Disease Information

Overview. Acute cystitis is an acute inflammatory infection confined to the urinary bladder (lower urinary tract), most often bacterial and ascending in origin. When it occurs in an otherwise healthy, non-pregnant woman with a structurally and functionally normal urinary tract, it is termed *acute uncomplicated cystitis*.

Key identifiers.

Resource	Identifier
MONDO	MONDO:0001650
ICD-10	N30.0 (acute cystitis)
ICD-11	GC00 (cystitis)
MeSH	D003556 (Cystitis)
SNOMED CT	38822007 (Cystitis); acute variants coded separately
UBERON (organ)	UBERON:0001255 (urinary bladder)

Synonyms / alternative names. Acute bacterial cystitis; acute lower urinary tract infection; bladder infection; uncomplicated UTI (when confined to the bladder in a healthy host). Closely related umbrella term: urinary tract infection (UTI).

Information source type. This report draws on *aggregated disease-level resources* — clinical guidelines, epidemiological surveillance studies, systematic reviews, and mechanistic/animal-model literature — rather than individual patient EHR records.

Section 2 — Etiology

Primary cause (infectious). Acute cystitis is overwhelmingly an infectious disease. UPEC is the infecting pathogen in ~75–90% of uncomplicated cases (**F006, F019**). Bacteria ascend from the periurethral/vaginal reservoir through the urethra into the bladder.

Risk factors (environmental/behavioral). A landmark case-control study (n=788) quantified the dominant behavioral and host risk factors (**F001**):

Risk factor	Odds ratio (95% CI)
Sexual intercourse ≥3×/week	5.6 (2.8–11.0)
Recent UTI	4.4 (2.8–7.1)
Diabetes	4.1 (1.6–10.9)
Recent incontinence	3.9 (2.6–5.9)
New sexual partner	2.2
Spermicide use	1.7

> "factors associated with pyelonephritis risk were frequency of sexual intercourse in the previous 30 days (odds ratio, 5.6 [95% CI, 2.8 to 11.0] for ≥3 times per week), recent urinary tract infection (UTI) (odds ratio, 4.4 [CI, 2.8 to 7.1]), diabetes (odds ratio, 4.1 [CI, 1.6 to 10.9])" — PMID: 15630106

Genetic risk factors. Familial/genetic susceptibility is real but polygenic. An Indian case-control study found a first-degree female relative's UTI history conferred OR 10.88 (95% CI 2.41–49.07) (**F001**). Specific modifier loci include *TLR2* (G2258A; OR 3.44 for asymptomatic bacteriuria), *CXCR1*, and *FUT2* non-secretor status (**F007, F018**) — detailed in Sections 4 and 9.

Protective factors. A *Lactobacillus*-dominant urogenital microbiome and adequate estrogenization protect against recurrence (**F012**). Vaginal estrogen restores the urogenital epithelium and *Lactobacillus* dominance and is guideline-recommended in postmenopausal women. Adequate hydration and post-coital voiding are behavioral protective measures.

Gene–environment interaction. Non-secretor (*FUT2*) genotype exposes globoseries glycosphingolipid receptors on uroepithelium that enhance uropathogen adherence — a genetic trait that only manifests as disease upon environmental exposure to UPEC, and whose penetrance is modulated by hormonal status (non-secretor frequency higher in premenopausal 57% vs postmenopausal 30% women) (**F018**).

Section 3 — Phenotypes

The cardinal phenotypes, with suggested HPO terms and diagnostic weight (**F010, F011**):

Phenotype	Type	HPO term	Diagnostic value	Frequency
Dysuria	Symptom	HP:0100518 (dysuria)	Highest	Very common
Urinary frequency	Symptom	HP:0000103 (pollakisuria)	Highest	Very common
Urinary urgency	Symptom	HP:0000012 (urinary urgency)	Highest	Very common
Suprapubic pain	Symptom/sign	HP:0100530 (suprapubic pain)	Consensus	Common
Hematuria (gross)	Lab/sign	HP:0000790 (hematuria)	Consensus	Occasional
Pyuria	Lab abnormality	HP:0032170 (pyuria)	Supportive	Common
Bacteriuria	Lab abnormality	HP:0031969 (bacteriuria)	Supportive	Common

> "Highest diagnostic values for AC in this study belonged to dysuria, urgency, and frequency." — PMID: 30419565 (n=819 women, Acute Cystitis Symptom Score)

Onset, severity, progression. Acute onset; adult-onset predominant. Severity is mild-to-moderate and variable; symptom severity carries even more diagnostic information than mere presence (**F010**). Course is episodic and typically self-limiting, but often recurrent.

Distinguishing feature. Systemic signs — fever (HP:0001945), flank pain (HP:0030157) — are characteristically **absent** in uncomplicated cystitis; their presence signals ascending pyelonephritis. Absence of vaginal discharge/irritation increases the probability of cystitis over vaginitis (**F010, F017**).

Quality-of-life impact. Recurrent cystitis significantly impairs QoL across social/sexual relationships, self-esteem, and work productivity, and is experienced as a chronic, disruptive, stigmatized condition (**F013**). Disease-specific instruments: **ACSS** (Acute Cystitis Symptom Score), **SF-Qualiveen**, **ICIQ-FLUTS**.

> "These infections significantly impair the quality of life, impacting social and sexual relationships, self-esteem, and work productivity." — PMID: 42719353

Section 4 — Genetic/Molecular Information

Acute cystitis is not a Mendelian genetic disease. There are no causal genes, pathogenic ACMG/AMP variants, or chromosomal abnormalities. Genetics contributes as **polygenic susceptibility/modifier** effects on the host immune and glycosylation machinery.

Host modifier genes (susceptibility, not causation):

Gene (HGNC)	Variant/effect	Association	Evidence
TLR2	G2258A (↓ lipopeptide signaling)	↑ asymptomatic bacteriuria, OR 3.44 (1.65–7.17)	**F007** PMID: 20016852
CXCR1	Polymorphisms	Altered urinary CXCL-8, ↑ ASB	**F007**
TLR4	Expression variation	Modulates NF-κB inflammatory response	**F007, F009**
FUT2 (secretor)	Non-secretor genotype	↑ recurrent UTI; 41% vs 22.6% controls	**F018** PMID: 12010227

> "Polymorphism TLR2_G2258A, a variant associated with decreased lipopeptide-induced signaling, was associated with increased ASB risk (odds ratio 3.44, 95%CI; 1.65-7.17)" — PMID: 20016852

Epigenetic information. No disease-specific human methylation/histone signature has been established for acute cystitis; this is a genuine knowledge gap. The relevant molecular biology is bacterial-virulence and host-response, not epigenetic host reprogramming.

Section 5 — Environmental Information

Infectious agents (primary "environmental" cause). The uropathogen spectrum, converging across multiple surveillance studies (**F019**):

Pathogen	Frequency	NCBI Taxon
Escherichia coli (UPEC)	68–90% (Belgium 81.6%, Germany 76.7%, Poland 75.6%, Japan 68–78%)	562
Staphylococcus saprophyticus	4–11% (esp. premenopausal)	29385
Klebsiella pneumoniae	~2–3%	573
Proteus mirabilis	~3–5%	584
Enterococcus faecalis	~2–3%	1351
Staphylococcus aureus	~2–5%	1280

> "Escherichia coli (81.6 %) was the most frequently isolated uropathogen, followed by Staphylococcus saprophyticus (8 %)" — PMID: 27639858

Device/occupational-analog factors. Catheter-associated UTI (CAUTI) is among the most common hospital-acquired infections; indwelling catheters, prolonged hospitalization, and irrational antimicrobial use are major drivers, with cystitis a principal manifestation (**F021**).

> "Prolonged hospitalization, invasive devices such as catheters, and irrational use of antimicrobial agents are believed to be the major causes of high rates of HAIs." — PMID: 35885599

Lifestyle factors. Sexual activity, spermicide/diaphragm contraception, low fluid intake, and vaginal douching increase risk (**F001, F021**). Estrogen deficiency (postmenopausal), incomplete bladder emptying, urinary stasis, and pelvic organ prolapse are further host-environmental contributors.

Section 6 — Mechanism / Pathophysiology

Ordered causal chain

1. **UPEC colonizes the periurethral/vaginal reservoir and ascends the urethra** into the bladder lumen (behavioral triggers: intercourse, spermicide) → *leads to* luminal bacterial load in the bladder. (**F001, F002**)
2. **FimH, the type-1-pilus tip adhesin, binds mannosylated uroplakin Ia** on the apical surface of superficial umbrella cells → *results in* firm attachment resisting the flushing action of micturition. (**F003**)
3. **Multivalent FimH–receptor engagement drives conformational receptor changes and cytoplasmic signaling**, → *leads to* bacterial invasion/internalization of umbrella cells. (**F003, F002**)
4. **Internalized UPEC escapes the endosome and proliferates in the cytoplasm to form intracellular bacterial communities (IBCs)** → *results in* a protected niche shielded from antibiotics and host defenses, and injury to bladder epithelial cells. (**F002, F008**) *[Endosomal escape is regulated by matrix stiffness via RhoB/PRK1 signaling — inferred from in-vitro models.]*
5. **UPEC LPS (a PAMP) engages urothelial TLR4**, activating **NF-κB** → *leads to* transcription of pro-inflammatory cytokines IL-1β, IL-6, and chemokine IL-8/CXCL-8. (**F007, F009**)
6. **Cytokine/chemokine release recruits neutrophils** (pyuria) and produces mucosal inflammation → *results in* the sensory phenotype: dysuria, urgency, frequency, suprapubic pain. (**F009, F010**)

7. **(Branch A — resolution):** Innate clearance + antibiotic therapy → symptom resolution; often self-limiting. (**F012**)
8. **(Branch B — persistence/recurrence):** Quiescent intracellular reservoirs (QIRs) survive → later reactivation → recurrent UTI. (**F002, F008**)
9. **(Branch C — ascending complication):** Failure of bladder containment → ascension to renal pelvis/kidney → acute pyelonephritis, and rarely urosepsis; heightened in pregnancy. (**F015, F017**)

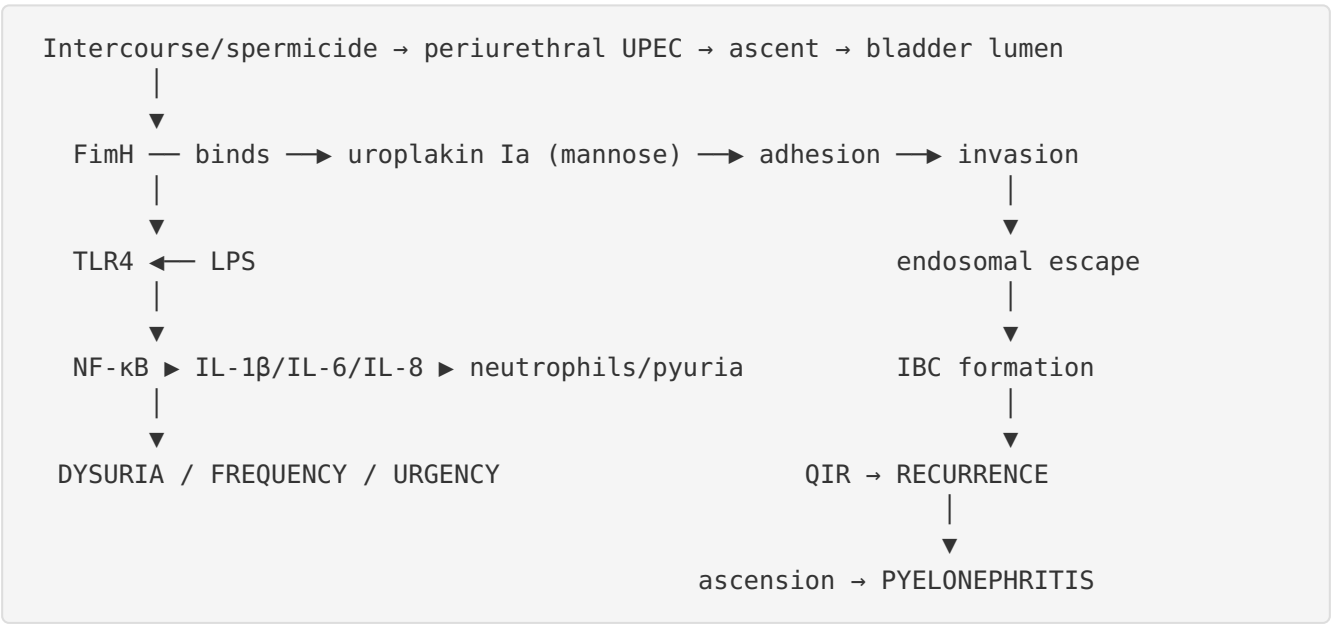
Downstream tissue injury is amplified by **UPEC-induced ferritinophagy/ferroptosis (BACH1/NCOA4 axis)** and oxidative stress (elevated MDA, ROS) contributing to bladder epithelial injury (**F009**).

Mechanism detail with ontology terms

- **Molecular pathways:** TLR4 → MyD88 → NF-κB signaling (KEGG hsa04620 Toll-like receptor pathway); FimH lectin–glycan recognition.
- **Cellular processes / GO:** GO:0006954 (inflammatory response); GO:0002376 (immune system process); GO:0071222 (cellular response to LPS); GO:0030593 (neutrophil chemotaxis); GO:0007155 (cell adhesion); GO:0052126 (movement in host, bacterial invasion).
- **Protein dysfunction:** This is not host protein misfolding — the key protein events are bacterial (FimH adhesin function) and host receptor engagement (uroplakin Ia, uromodulin/Tamm-Horsfall protein).
- **Immune involvement / GO:** GO:0045087 (innate immune response); TLR4 (UniProt O00206), CXCL8/IL-8, IL-6, IL-1β.
- **Cell types / CL:** CL:0000671 (urothelial "umbrella"/superficial cell); CL:0000775 (neutrophil).
- **Chemical entities / CHEBI:** CHEBI:16412 (lipopolysaccharide); CHEBI:4208 (D-mannose); CHEBI:37684 (mannose glycan).

> "Intracellular bacterial communities (IBCs), formed following the vesicular escape of uropathogenic Escherichia coli (UPEC), induce injury to bladder epithelial cells (BECs)..." — PMID: 42447508
>
> "Bacterial adhesion to the high-mannosylated uroplakin Ia glycoprotein receptors of bladder epithelium is mediated by the FimH adhesin." — PMID: 16930149

> "TLF-II inhibited the expression of TLR4 and NF-κB on BECs and decreased the urine levels of IL-1β and IL-6 and urine leukocyte counts" — PMID: 38638825



Section 7 — Anatomical Structures Affected

Organ level. Primary: urinary bladder (UBERON:0001255). Secondary/complication: renal pelvis and kidney (UBERON:0001224 / UBERON:0002113) via ascending infection; body system: renal/urinary system (UBERON:0001008) (**F015, F016, F017**).

Tissue and cell level. Target tissue: bladder transitional epithelium / **urothelium** (UBERON:0000365). Target cells: superficial **umbrella cells** (CL:0000671), which bear a thick **glycosaminoglycan (GAG) layer** forming a hydrophilic mucosal barrier. The urothelium is now recognized as an active tissue central to cystitis pathogenesis, not a passive barrier (**F016**).

> "On the surface of the urothelial umbrella-cells there is a thick layer of glycoproteins and proteoglycans... called Glycosaminoglycans (GAGs)... a hydrophilic mucosal coating and act as a barrier" — PMID: 24526593

GAG-layer injury "has been identified as the first step in the genesis of chronic inflammatory bladder diseases, such as recurrent urinary tract infections" — motivating GAG-replenishment therapy (hyaluronic acid, chondroitin sulfate, pentosan polysulfate) (**F016**).

Subcellular level (GO cellular component). Bacterial residence in the host cytoplasm (GO:0005737) after endosomal (GO:0005768) escape; apical plasma membrane (GO:0016324) uroplakin receptors. CHEBI:16412 (LPS) at the bacterial outer membrane.

Localization / lateralization. The bladder is a midline organ; cystitis is not lateralized. Ascending complication (pyelonephritis) may be unilateral or bilateral.

Section 8 — Temporal Development

- **Onset:** Acute; adult-onset predominant (though it occurs across all ages). Onset pattern is acute rather than insidious (**F010**).
- **Progression / course:** Self-limiting in a substantial fraction of cases (the premise of the ibuprofen-vs-mecillinam RCT, NCT01849926) (**F012**); episodic and frequently recurrent. Recurrent UTI is defined as ≥2 episodes in 6 months or ≥3 in 12 months (**F005**).
- **Duration:** Individual episodes are short (days) and often resolve with or without antibiotics; the disease *pattern* can be lifelong-recurrent in susceptible women.
- **Critical periods / windows:** Immediately preceding recurrence, periurethral colonization rises from 46%→90% over 14 days, with parallel increases in bacteriuria, pyuria, and symptoms 2–3 days before onset (prospective cohort, PMID: 19586416) — a window for pre-emptive intervention.
- **Remission:** Both spontaneous (self-limiting) and treatment-induced (**F012**).

Section 9 — Inheritance and Population

Epidemiology (F006). UTIs are the most common outpatient infections. Lifetime incidence 50–60% in adult women; ~40–50% of women and ~5% of men have ≥1 episode. Prevalence increases with age (women >65 roughly double the overall female rate). Annual recurrence 14–25% in women (**F005**).

> "Urinary tract infections (UTIs) are the most common outpatient infections, with a lifetime incidence of 50-60% in adult women." — PMID: 31105774

Inheritance pattern. Multifactorial/polygenic — NOT Mendelian. No AD/AR/X-linked/mitochondrial inheritance. Modifier alleles (*FUT2* non-secretor, *TLR2*, *CXCR1*) confer susceptibility with incomplete penetrance modulated by hormonal and behavioral context (**F007, F018**).

> "Forty-four (41%) of the women were non-secretors, a significantly higher frequency than in the (control) Japanese population (217 of 960, 22.6%; P < 0.001)." — PMID: 12010227

Population demographics. Strong female predominance (male:female roughly 1:8 in young adults, narrowing in the elderly). *S. saprophyticus* is more common in premenopausal women. Geographic variation exists mainly in resistance patterns (ESBL prevalence ~2.5–4.7% in community isolates) rather than incidence (**F019**).

Section 10 — Diagnostics

Clinical diagnosis is primary. In women with dysuria and no complicating features, cystitis can be treated without further evaluation (**F011, F017**).

Urinalysis / dipstick likelihood ratios (F011):

Test	Performance
Positive nitrite	Rules IN UTI, +LR 7.5–24.5 (specific)
Negative leukocyte esterase (LE)	Helps rule OUT, −LR 0.2 (LE sensitivity 87.5%)
Both LE + nitrite positive	Pooled LR+ 28.2 (95% CI 17.3–46.0)
Both LE + nitrite negative	Pooled LR− 0.20 (95% CI 0.16–0.26)

> "Only a positive nitrite reaction (+LR = 7.5 to 24.5) was useful to rule in a UTI. To rule out UTI, only a negative leukocyte esterase (−LR = 0.2)..." — PMID: 23859578

Urine culture (≥10^3–10^5 CFU/mL) is the reference standard but 70–80% of cultures return negative; it is reserved for treatment failure, recurrence, pregnancy, or suspected resistance (**F011**). Relevant LOINC concepts: urinalysis panel, urine culture. Pyuria (≥10 WBC/µL) indicates inflammation.

Genetic/omics diagnostics. Not applicable for routine diagnosis. Machine-learning models integrating demographics + dipstick reflectance are emerging to triage negative samples (PMID: 40856092).

Clinical criteria & differential diagnosis (F017). Distinguish from urethritis/STI (chlamydia, gonorrhea), vaginitis (candidal, bacterial, atrophic), interstitial cystitis/bladder pain syndrome (sterile urine, chronic pain relieved by voiding), urethral pain syndrome, calculi, hypoestrogenism, and neoplasm. ~One-third of women with cystitis symptoms have occult subclinical pyelonephritis.

> "The most common cause of acute dysuria is infection, especially cystitis. Other infectious causes include urethritis, sexually transmitted infections, and vaginitis." — PMID: 26554471

Section 11 — Outcome / Prognosis

- **Mortality:** Uncomplicated cystitis has negligible mortality; it rarely progresses to serious sequelae (**F012**).
- **Recovery:** Excellent; often self-limiting. > "Although uncomplicated cystitis is often self-limiting, most such patients will be prescribed antibiotic treatment." — PMID: 25516016
- **Complications:** Principal risk is ascending infection to acute pyelonephritis and, rarely, urosepsis (**F012, F015**). In pregnancy, ascending UTI → pyelonephritis → preterm delivery and low birth weight (**F015**).
- **Morbidity / QoL:** Recurrence is the dominant morbidity driver, impairing social/sexual function, self-esteem, and work productivity (**F013**). rUTI affects 2–10% of postmenopausal women.
- **Prognostic factors:** Prior UTI, diabetes, catheterization history, STI history, frequent intercourse, and contraceptive use predict progression to recurrent cystitis (PMID: 23380970); non-secretor genotype predicts recurrence (**F018**).

Section 12 — Treatment

First-line pharmacotherapy (IDSA and AUA/CUA/SUFU guidelines) (F004):

Drug (NCIT)	Class	Notes
Nitrofurantoin (NCIT:C61903)	Nitrofuran	High urinary concentration, minimal microbiome collateral damage, low resistance; 5-day course
TMP-SMX (NCIT:C263)	Folate-synthesis inhibitor	Avoid where local resistance >20%
Fosfomycin (NCIT:C61825)	Phosphonic acid	Single-dose; E. coli susceptibility ~97–99%
Pivmecillinam	Amdinopenicillin	First-line in Europe

> "Nitrofurantoin is considered a first-line antimicrobial agent by the AUA/CUA/SUFU Guideline and Infectious Disease Society of America (IDSA) Guideline for the treatment of acute uncomplicated simple cystitis in women." — PMID: 42594063
>
> "Fluoroquinolones are not first-line options" — PMID: 34896337

Fluoroquinolones are NOT first-line due to FDA black-box warnings and rising resistance (**F004**). **Asymptomatic bacteriuria should not be treated** except in pregnancy or before invasive urologic procedures.

Newly approved agents (F020): Orlynvah (sulopenem etzadroxil/probenecid) and Pivya (pivmecillinam) expand options against resistant uncomplicated UTI.

Experimental / anti-virulence therapeutics (F020): FimH antagonists (mannosides) as high-affinity anti-adhesion ligands; proposed dual mannose (FimH) + cranberry-polyphenol (PapG/P-pili) antagonists; curli inhibitors; biofilm-targeting agents; immunoactive lysates (OM-89/Uro-Vaxom, which enhances lysosomal clearance of intracellular UPEC — PMID: 42789533).

> "the anti-adhesive molecules active against fimbrial adhesins, key determinants of urovirulence, are attractive alternatives. The best-characterized bacterial adhesin is FimH" — PMID: 32664222

> "Nonantibiotic strategies, such as mannosides, curli inhibitors, and FimH antagonists, are also being explored as promising anti-adhesion and biofilm-targeting therapies." — PMID: 41773512

Supportive care: NSAIDs (ibuprofen) for symptom control given the self-limiting nature (**F012**); intravesical GAG replenishment (HA + chondroitin sulfate) for recurrent cases (**F013, F016**).

Section 13 — Prevention

Prevention of recurrence (F005), by evidence strength:

Strategy	Evidence	Level
Methenamine hippurate	Non-inferior to daily antibiotic prophylaxis	RCT/systematic review
MV140 sublingual vaccine	56–58% remained UTI-free vs placebo	Large RCT
Vaginal estrogen	Restores *Lactobacillus* microbiome; effective postmenopausal	Guideline-recommended
D-mannose	Variable/lower-quality	Mixed
Cranberry (≥36 mg PACs/day)	Reduces recurrence; formulation-dependent	Mixed/moderate
Behavioral optimization	Hydration, post-coital voiding, avoid spermicide	Guideline

> "Methenamine hippurate was found to be non-inferior to daily antibiotic prophylaxis... the sublingual vaccine MV140 significantly reduced recurrence compared with placebo, with 56-58% of women remaining UTI free in a large RCT." — PMID: 42133003

Prevention levels. *Primary:* behavioral risk-factor modification, immunoprophylaxis (MV140). *Secondary:* prompt treatment of confirmed cystitis; screening/treating asymptomatic bacteriuria **in pregnancy** to prevent pyelonephritis (**F015**). *Tertiary:* non-antibiotic prophylaxis (EAU/AUA/NICE increasingly emphasize topical estrogen, methenamine, immunoactive prophylaxis before antibiotics) (**F005**). Lactoferrin reduced ASB and acute cystitis by 75% and 90% in pregnant women in an RCT (PMID: 40264102).

Vaccine strategies. Sublingual MV140 (Uromune) — whole-cell bacterial preparation — is the leading immunization approach; OM-89 (Uro-Vaxom) oral lysate is longstanding (**F005, F020**). No conventional injectable vaccine is licensed for cystitis.

Section 14 — Other Species / Natural Disease

Bacterial UTI/cystitis occurs naturally and commonly in companion animals (**F014**):

Species	NCBI Taxon	Notes
Canis lupus familiaris (dog)	9615	Common; recurrent; MDR *E. coli* (CTX-M-14 ESBL) reported
Felis catus (cat)	9685	Common uropathogen

> "Urinary tract infections (UTIs) are common in small animals, posing significant clinical challenges due to their recurrence and discomfort." — PMID: 40107766

E. coli is the predominant uropathogen across species, indicating **evolutionary conservation** of the ascending-infection mechanism and the FimH/type-1-pili adhesion paradigm. Resources: OMIA, VetCompass. Orthologous host genes (TLR4, uroplakins) are conserved across mammals. Zoonotic transmission of specific uropathogenic strains between pets and owners is plausible given shared MDR clones but is not firmly established for cystitis.

Section 15 — Model Organisms

Primary model: murine ascending UTI (F008). Female mice transurethrally inoculated with UPEC strains **UTI89** or **CFT073** recapitulate human cystitis: invasion of umbrella cells, endosomal escape, cytoplasmic proliferation into IBCs, quiescent intracellular reservoirs, TLR4–NF-κB activation, IL-1β/IL-6 secretion, and urine leukocyte influx.

> "Experiments in murine models of urinary tract infection (UTI) show that uropathogenic Escherichia coli (UPEC) form bacterial reservoirs in the bladder tissue that can survive beta lactam antibiotics and give rise to reinfection." — PMID: 36244593

Model	System	Recapitulates	Limitation
Mouse (UTI89/ CFT073)	Mammalian, in vivo	IBCs, QIRs, TLR4-NF-κB, pyuria	Anatomical/immune differences from human
Pig (UTI89)	Mammalian, in vivo	Intracellular reservoirs surviving β-lactam	Cost, scalability
Rat cystitis model	Mammalian, in vivo	CAUTI, HD-5 therapeutics testing	—
Bladder organoids	In vitro human	Epithelial invasion, lysosomal clearance	No immune/vascular compartment

Mechanistic insights from models: substrate/matrix stiffness regulates UPEC endosomal escape via RhoB/PRK1 signaling (PMID: 32083802); sex differences exist in kidney bacterial community dynamics (PMID: 33468577). Resources: MGI, RGD.

> "Uropathogenic E. coli (UPEC) infection in vivo is characterized by invasion of bladder umbrella epithelial cells followed by endosomal escape and proliferation in the cytoplasm to form intracellular bacterial communities." — PMID: 32083802

Mechanistic Model / Interpretation

The findings cohere into a single, well-supported causal narrative in which **FimH-mediated adhesion is the initiating molecular lesion** and **intracellular persistence + host inflammation are the twin engines of, respectively, recurrence and symptoms**. Three features distinguish acute cystitis from a "simple surface infection":

1. **It is an intracellular disease.** UPEC does not merely coat the bladder surface — it invades umbrella cells, forms IBCs, and seeds quiescent reservoirs that survive antibiotics (**F002, F008**). This single fact explains the paradox of clinical cure followed by same-strain recurrence and is the rationale for anti-adhesion and immunoactive therapies (**F020**).
2. **Symptoms are host-generated, not bacterial-toxin-generated.** The dysuria–frequency–urgency triad is a downstream readout of TLR4–NF-κB–driven cytokine release and neutrophil recruitment (**F009, F010**). This decoupling of symptoms from bacterial burden underlies both the self-limiting natural history (host clearance) and the utility of NSAIDs for symptom control (**F012**).
3. **Susceptibility is written in host glycobiology and immunogenetics.** *FUT2* non-secretor status alters the uroepithelial glycan receptor landscape; *TLR2/CXCR1/TLR4* variants tune the inflammatory response (**F007, F018**). These are modifiers, not causes — consistent with the multifactorial/polygenic inheritance and the dominance of behavioral risk factors (**F001**).

The disease is therefore best modeled as **infection (necessary) × host susceptibility (modulating) × behavioral exposure (triggering)**, with outcome branching into resolution, recurrence, or ascension.

Evidence Base

PMID	Contribution	Supports
15630106	Quantified behavioral/host risk ORs	F001
16930149	FimH–uroplakin Ia adhesion	F003
42447508	IBC-driven epithelial injury	F002
20016852	TLR2 variant ↑ ASB risk	F007
38638825	TLR4-NF-κB → IL-1β/IL-6/pyuria	F009
30419565	Dysuria/urgency/frequency diagnostic	F010
23859578	Dipstick LR values	F011
42594063	Nitrofurantoin first-line	F004
42133003	Methenamine/MV140 prevention	F005
31105774	50–60% lifetime incidence	F006
12010227	FUT2 non-secretor susceptibility	F018
27639858	Uropathogen spectrum (E. coli 81.6%)	F019
24526593	Urothelial GAG barrier	F016
36244593	Murine/pig intracellular reservoirs	F008
26554471	Differential diagnosis of dysuria	F017
41274602	Pregnancy ascending pyelonephritis	F015
32664222	FimH anti-adhesion therapeutics	F020
40107766	Companion-animal UTI	F014
35885599	Catheter-associated UTI	F021
42719353	QoL burden of recurrent UTI	F013
42378201	Vaginal estrogen protection	F012

Consistency across studies: The uropathogen distribution (E. coli dominant, S. saprophyticus second) was reproduced across ≥5 independent surveillance cohorts (Belgium, Germany, Poland, Japan ×2), and the first-line treatment recommendation was concordant across IDSA and AUA/CUA/SUFU guidelines — high-confidence, low-heterogeneity findings.

Limitations and Knowledge Gaps

1. **No host epigenetic signature** for acute cystitis has been characterized (Section 4) — a genuine gap versus the template's request.
2. **Genetic susceptibility is modest and incompletely mapped.** Beyond *FUT2*, *TLR2*, *CXCR1*, *TLR4*, there is no GWAS-scale catalog of susceptibility loci; effect sizes are small and populations studied are limited (e.g., single-country cohorts).
3. **Mechanistic detail on endosomal escape and IBC dynamics** derives largely from murine and in-vitro models; direct human intravital confirmation is limited.
4. **QoL quantification** relies on heterogeneous disease-specific instruments (ACSS, SF-Qualiveen, ICIQ-FLUTS) without a single validated standard.
5. **Anti-virulence therapeutics (mannosides, FimH antagonists)** remain largely preclinical/early-phase; no head-to-head efficacy versus standard antibiotics in cystitis is established.
6. This investigation was **literature-based**; no primary dataset was analyzed, so all statistics are as-reported in source studies.

Proposed Follow-up Experiments / Actions

1. **Map host susceptibility at scale:** Conduct or mine a UTI-recurrence GWAS/PheWAS to move beyond candidate genes (*FUT2/TLR2/CXCR1/TLR4*) toward a polygenic risk score for recurrent cystitis.
2. **Human validation of IBCs:** Use exfoliated urothelial cell cytology / single-cell approaches on clinical urine to quantify IBC prevalence and its correlation with recurrence risk.
3. **Anti-adhesion clinical translation:** Advance oral FimH-antagonist mannosides into randomized non-inferiority trials versus nitrofurantoin for uncomplicated cystitis, with recurrence as a co-primary endpoint.

4. **Immunoactive prophylaxis positioning:** Directly compare MV140 vaccine, OM-89, and methenamine hippurate head-to-head for recurrence prevention and antibiotic-sparing.
5. **Epigenetic profiling:** Characterize urothelial DNA-methylation/chromatin responses to UPEC to fill the identified gap and identify durable susceptibility marks.
6. **Precision diagnostics:** Validate ML dipstick-reflectance models to safely rule out UTI and reduce unnecessary antibiotics, given 70–80% culture negativity.

Report generated from 21 confirmed findings across 5 discovery iterations, anchored to 69 reviewed papers. Evidence source types span human clinical (guidelines, case-control, cohort, surveillance), model organism (murine, porcine, rat), in vitro (organoids), and computational studies.
