Acute Pyelonephritis (MONDO:0003529): A Comprehensive Disease Characterization

Infectious Disease — Disease Knowledge Base Research Report

Summary

Acute pyelonephritis (APN) is an acute pyogenic bacterial infection of the renal parenchyma and pelvicalyceal system, overwhelmingly caused by ascending uropathogenic *Escherichia coli* (UPEC). It is not a Mendelian genetic disease; rather, whether a lower urinary tract infection (UTI) ascends and establishes symptomatic parenchymal kidney infection is determined chiefly by the interplay between bacterial virulence factors and the **host innate immune response**. UPEC adhesins — P-fimbriae binding uroepithelial glycosphingolipids and type 1 pilus FimH binding renal desmoglein-2 (DSG2) — anchor bacteria in the kidney and trigger Toll-like receptor 4 (TLR4)→IRF3 signaling and IL-8/CXCR1-mediated neutrophil recruitment. Neutrophils are the decisive clearance effectors: when this axis is intact, infection is contained (asymptomatic bacteriuria); when it is defective (IRF3 promoter variants, IL-8/*CXCL8* rs4073, low CXCR1 expression), bacteria invade the parenchyma, producing symptomatic pyelonephritis and, potentially, permanent renal scarring.

Clinically, APN presents acutely with fever, flank pain, costovertebral angle tenderness, and pyuria, most often in women (anatomic predisposition) and infants, with a distinctly bimodal and female-predominant epidemiology whose incidence roughly doubled between 2000 and 2018 in population data. Most uncomplicated disease is curable with prompt antibiotics — a landmark trial establishes that **7 days of ciprofloxacin is non-inferior to 14 days** in women — but severe complications (urosepsis, emphysematous pyelonephritis, renal/perinephric abscess, scarring and chronic kidney disease) cluster in patients with diabetes, urinary obstruction, pregnancy, and vesicoureteral reflux (VUR). Rising fluoroquinolone resistance and

extended-spectrum β-lactamase (ESBL) production in community *E. coli* now constrain empirical therapy, driving interest in carbapenem-sparing agents (ceftazidime-avibactam) and non-antibiotic prevention.

Prevention is anchored in **screen-and-treat of asymptomatic bacteriuria (ASB) in pregnancy**, source control of obstruction, and evidence-based recurrence prophylaxis — antimicrobial prophylaxis in high-grade VUR (RIVUR trial: 50% reduction), and non-antibiotic options with RCT support including the sublingual vaccine MV140, methenamine hippurate, and vaginal estrogen. Biomarkers such as urinary NGAL (LCN2) and procalcitonin aid diagnosis and predict scarring, while DMSA scintigraphy remains the reference standard for detecting parenchymal involvement. This report synthesizes 13 confirmed findings from 69 reviewed papers into a mechanistic and clinical portrait suitable for populating a structured disease knowledge base.

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1. Disease Information

Definition. Acute pyelonephritis is an acute suppurative bacterial infection of the renal parenchyma, tubules, and renal pelvis (upper urinary tract), typically arising by ascent of uropathogens from the bladder. It sits at the severe end of the UTI spectrum, above asymptomatic bacteriuria (ASB) and lower-tract cystitis. It is a form of "complicated" or "febrile" UTI when accompanied by systemic signs.

Key identifiers.

Resource	Identifier
MONDO	MONDO:0003529 (acute pyelonephritis)
MeSH	Pyelonephritis (D011704); Pyelonephritis, Xanthogranulomatous (D058489)
ICD-10	N10 (Acute tubulo-interstitial nephritis / acute pyelonephritis); O23.x for pregnancy-associated
ICD-11	GB51 (Acute pyelonephritis)
SNOMED CT	45816000 (Pyelonephritis); acute pyelonephritis subtype
OMIM / Orphanet	Not a Mendelian disorder; no dedicated OMIM phenotype MIM. Host susceptibility loci exist (see §4). Not an Orphanet rare disease per se.

Synonyms / alternative names. Acute infective tubulo-interstitial nephritis; upper urinary tract infection; acute febrile UTI; ascending pyelonephritis. Variant/related entities: **emphysematous pyelonephritis (EPN)**, **xanthogranulomatous pyelonephritis (XGP)**, **acute lobar nephronia / acute focal bacterial nephritis (ALN/AFBN)**, **pyonephrosis**, and **perinephric abscess**.

Data provenance. Evidence in this report is drawn from **aggregated disease-level resources** — population registries (e.g., a 19-year Danish cohort), prospective clinical cohorts, randomized controlled trials, systematic reviews/meta-analyses, and mechanistic model-organism and in-vitro studies — supplemented by EHR-derived cohort studies. It is not derived from a single individual patient.

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2. Etiology

Primary cause — infectious. APN is overwhelmingly bacterial and ascending. **Uropathogenic *E. coli* (UPEC)** is the dominant pathogen. In a US prospective study (2013–2014) of adults with culture-confirmed APN, *E. coli* grew in **86.9% (453/521)** of cases (PMID: 27532362). Other uropathogens include *Klebsiella pneumoniae*, *Proteus mirabilis* (associated with struvite/staghorn calculi and XGP), *Enterococcus*, *Pseudomonas*, and, in specific contexts, *Staphylococcus saprophyticus* and *Candida*. Hematogenous seeding (e.g., *Staphylococcus aureus*) is a less common alternative route.

Risk factors.

Environmental / clinical (host): - **Female sex** — short urethra and perineal proximity favor ascent. Strong female predominance across all age strata (PMID: 38020186). - **Pregnancy** — ureteral dilation, urinary stasis, and ASB markedly raise ascending-infection risk (PMID: 41274602). - **Diabetes mellitus** — the dominant risk factor for necrotizing/emphysematous forms (63–76% of EPN series) (PMID: 42221797, PMID: 41836219). - **Urinary obstruction / stones** — present in ~46% of severe EPN (PMID: 42221797); staghorn calculi underlie XGP. - **Vesicoureteral reflux (VUR)** and **bladder-bowel dysfunction (BBD)** — key pediatric risk factors and drivers of scarring (PMID: 35928985). - Infancy/early childhood, instrumentation/catheterization, immunosuppression, prior UTI, and sexual activity.

Genetic (host susceptibility — not causal Mendelian): - **IRF3 promoter polymorphisms** associated with symptomatic kidney infection vs asymptomatic carriage (PMID: 20886096). - **IL-8 / *CXCL8* rs4073 (−251A>T)** associated with pediatric parenchymal renal infection (PMID: 21042230). - Low **CXCR1** expression predisposes to pyelonephritis and scarring (PMID: 11817650).

Protective factors. Intact innate immunity (functional TLR4→IRF3 and IL-8/CXCR1 neutrophil axis); urinary **neutrophil extracellular traps (NETs)** that block ascension (PMID: 39321268); adequate hydration/urine flow; absence of obstruction; and, for recurrence, vaginal estrogen in postmenopausal women and prophylactic strategies (§13). No well-established protective germline variant is defined; conceptually, "high" innate-signaling genotypes are protective.

Gene–environment interactions. Host genotype modulates the environmental exposure (bacterial colonization): the same UPEC exposure yields ASB in hosts with robust IRF3/IL-8/CXCR1 signaling but ascending symptomatic pyelonephritis in hosts with attenuated signaling. Diabetes (environmental/metabolic) interacts with tissue susceptibility to produce necrotizing EPN. Androgen status interacts with macrophage polarization to modulate post-infection scarring (PMID: 32849562).

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3. Phenotypes

Phenotype	Type	Suggested HPO	Frequency / notes
Fever	Symptom/sign	HP:0001945	Very frequent; hallmark of "febrile UTI"
Flank / loin pain	Symptom	HP:0030157 (flank pain)	Frequent; often unilateral
Costovertebral angle tenderness	Clinical sign	—	Characteristic exam finding
Dysuria / urinary frequency / urgency	Symptom	HP:0100518 (dysuria)	Common (lower-tract overlap)
Nausea and vomiting	Symptom	HP:0002018 / HP:0002013	Common, especially children
Pyuria (leukocyturia)	Lab abnormality	HP:0032453 (pyuria)	Near-universal; basis of leukocyte-esterase/NET dipstick (PMID: 39321268)
Bacteriuria	Lab abnormality	HP:0012461 (bacteriuria)	Defining; $\geq 10^5$ CFU/mL
Leukocytosis / elevated CRP, PCT	Lab abnormality	HP:0001974 (leukocytosis)	Systemic inflammation; PCT/ uNGAL predict severity/scarring
Hematuria	Lab/sign	HP:0000790	Variable
Sepsis / septic shock	Clinical complication	HP:0100806 (sepsis)	~72% septic shock in ICU EPN cohort (PMID: 42221797)
Renal scarring	Structural sequela	HP:0000800 region / scarring	Long-term; DMSA-defined

Onset / severity / progression. Onset is **acute** (hours to a few days). Age of onset is **bimodal**: high in infancy (especially girls), then predominant in reproductive-age women, with a further rise in the elderly. Severity is **variable** — from outpatient-manageable uncomplicated APN to fulminant urosepsis. Course is typically **self-limited with treatment**, but delayed therapy (>72 h) increases permanent scarring (PMID: 27748543).

Quality-of-life impact. Acute APN causes marked short-term morbidity (hospitalization, pain, fever, work loss). Recurrent UTI/pyelonephritis substantially impairs quality of life and drives major antibiotic use (PMID: 42225392). Post-pyelonephritic scarring can progress to hypertension and CKD, with lasting functional impact.

4. Genetic / Molecular Information

APN has **no causal Mendelian gene**; it is a multifactorial infectious disease with host **susceptibility loci** that shift the balance between asymptomatic bacteriuria and symptomatic parenchymal infection.

Susceptibility genes / variants (host innate immunity):

Gene (HGNC)	Variant / feature	Effect	Evidence
IRF3	Promoter polymorphism; disease genotype lowers promoter activity	Reduced type I IFN/innate signaling → symptomatic kidney infection	PMID: 20886096
CXCL8 (IL-8)	rs4073 (−251A>T)	Altered neutrophil chemokine signaling → parenchymal renal infection in children	PMID: 21042230
CXCR1	Low receptor expression	Impaired neutrophil clearance → pyelonephritis + scarring	PMID: 11817650
TLR4	Signaling capacity	Modulates mucosal response (high response → symptomatic; low → ASB)	PMID: 21042230

Variant class: regulatory/promoter SNPs and expression-modulating polymorphisms (not protein-truncating). Origin: **germline** host variants (susceptibility), distinct from the **bacterial genome** (virulence). Functional consequence: partial **loss of innate signaling function** predisposing to ascension. In PMID: 21042230, among TLR4/IL-8/CXCR1/CXCR2 SNPs tested in children with APN/ALN (VUR excluded), "*only IL-8 (rs4073, −251A>T) showed significant differences in genotype and allele frequency between the control and APN or ALN cases.*"

Bacterial "virulence genotype." Disease is strongly shaped by the pathogen genome: *fim* (type 1 pili/FimH), *pap* (P-fimbriae), *hly* (α-hemolysin), and siderophore systems. ESBL genes (e.g., *bla*CTX-M) and fluoroquinolone-resistance determinants convert treatable disease into refractory disease (PMID: 27532362); ST131-H30Rx clones carry virulence factors linked to recurrence (PMID: 40926251).

Modifier genes / epigenetics / chromosomal abnormalities. Androgen-responsive pathways modify macrophage polarization and scarring (PMID: 32849562). No disease-specific DNA-methylation signature or recurrent chromosomal abnormality is established for APN; CAKUT (congenital anomalies of kidney/urinary tract) predispose anatomically but did not explain the observed incidence rise (PMID: 38020186).

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5. Environmental Information

- **Infectious agents (NCBI Taxonomy):** *Escherichia coli* (txid562) — dominant; *Klebsiella pneumoniae* (txid573); *Proteus mirabilis* (txid584); *Enterococcus faecalis* (txid1351); *Pseudomonas aeruginosa* (txid287); *Candida* spp. (fungal, in diabetics/instrumented patients).
- **Environmental/metabolic factors:** Diabetes mellitus and hyperglycemia (tissue substrate for gas-forming necrotizing EPN); urinary catheters/instrumentation (nosocomial exposure); obstruction/stones (stasis).
- **Lifestyle factors:** Sexual activity, spermicide/diaphragm use, inadequate fluid intake, and delayed voiding increase lower-UTI and ascension risk. Increased fluid intake benefits those with low baseline intake (PMID: 42225392).
- **Occupational/toxin exposures:** No specific occupational toxin is causally linked; APN is infection-driven.

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6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Periurethral/fecal UPEC colonization** of the introitus/urethra **leads to** bladder colonization (ascending route).

2. Bladder UPEC express **type 1 pili (FimH)** and **P-fimbriae (PapG)**; FimH binds **mannosylated desmoglein-2 (DSG2)** on renal epithelium and P-fimbriae bind uroepithelial glycosphingolipids, which **results in** adhesion and ascent up the ureter to the renal pelvis and collecting ducts (demonstrated in C3H/HeN mice; $FimH^-$ mutants cannot establish kidney infection) (PMID: 33513212).
3. Adhesion and bacterial products (LPS, hemolysin) **activate TLR4 on tubular/uroepithelial cells**, which **leads to IRF3-dependent** innate signaling and **IL-8/CXCL8 secretion** (branch point A) (PMID: 20886096, PMID: 21042230).
4. IL-8 engaging **CXCR1** on neutrophils **results in** massive **neutrophil recruitment** across the uroepithelium into the parenchyma and urine — the decisive effector step (PMID: 11817650).
5. **Branch A — effective clearance:** Neutrophils phagocytose bacteria, release granules/ROS, and form **NETs** (also present in healthy urine), which **results in** bacterial containment → **asymptomatic bacteriuria or resolution** and a positive leukocyte dipstick (PMID: 39321268, PMID: 42524556).
6. **Branch B — defective clearance** (low CXCR1, IRF3/IL-8 risk genotypes): impaired neutrophil recruitment/function **leads to** parenchymal bacterial proliferation, abscess formation, and **symptomatic acute pyelonephritis** (PMID: 11817650, PMID: 20886096).
7. Persistent/dysregulated neutrophil activation **results in** collateral tissue injury via **ROS, proteases, S100A8/A9, and NET-associated mediators**, which **leads to** tubulointerstitial damage (double-edged effector) (PMID: 42524556).
8. Injury plus **androgen-influenced polarization of activin-A–producing macrophages leads to** fibrogenic remodeling and **permanent renal scarring** (post-pyelonephritic scarring) — inferred from mouse models (PMID: 32849562, PMID: 42524556).
9. In **diabetic/obstructed** hosts (branch C), high tissue glucose and impaired perfusion **result in** gas-forming necrotizing infection = **emphysematous pyelonephritis**, which **leads to** sepsis/septic shock and, without source control, death (PMID: 42221797).
10. Systemically, bacteremia and cytokine release **result in** SIRS/**urosepsis**; scarring over time **leads to** hypertension and **chronic kidney disease** (PMID: 40022942).

Detail by category

- **Molecular pathways:** TLR4 → MyD88/TRIF → **IRF3** (type I IFN) and NF-κB → IL-8/CXCL8; IL-8–CXCR1/CXCR2 chemotaxis. (Reactome: Toll-like receptor cascades; KEGG hsa04620.)

- **Cellular processes:** Innate inflammation, neutrophil chemotaxis/phagocytosis, NETosis, ROS burst, apoptosis/necrosis of tubular cells, macrophage polarization, fibrosis.
- **Protein dysfunction:** Bacterial FimH lectin domain gains pathogenic function by binding host DSG2; a mannose-binding-pocket mutation abolishes binding (PMID: 33513212). Host risk = reduced IRF3 promoter activity / low CXCR1.
- **Immune involvement:** Predominantly **innate** (neutrophils, macrophages, epithelial sensing). Not autoimmune.
- **Tissue-damage mechanisms:** Oxidative stress (ROS), protease-mediated injury, NET-associated cytotoxicity, ischemia (obstruction), necrosis, and fibrogenesis.
- **Molecular profiling:** Biomarkers up in disease include **NGAL/LCN2**, procalcitonin, CRP, and S100A8/A9 (calprotectin). NGAL is itself a bacteriostatic (iron-sequestering) innate effector.

Suggested ontology terms. GO biological process: neutrophil chemotaxis (GO:0030593), defense response to bacterium (GO:0042742), Toll-like receptor signaling pathway (GO:0002224), neutrophil extracellular trap formation (GO:0140494), response to lipopolysaccharide (GO:0032496). CL cell types: neutrophil (CL:0000775), macrophage (CL:0000235), kidney collecting duct epithelial cell (CL:1000454), renal proximal tubule epithelial cell (CL:1000838). CHEBI: reactive oxygen species (CHEBI:26523), lipopolysaccharide (CHEBI:16412).

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7. Anatomical Structures Affected

- **Primary organ:** Kidney (UBERON:0002113) — specifically **renal parenchyma/cortex** (UBERON:0001225), **renal medulla** (UBERON:0000362), **renal pelvis** (UBERON:0001224), and **collecting duct** (UBERON:0001232), the principal site of FimH–DSG2 adhesion.
- **Secondary/complications:** Perinephric space (perinephric abscess), ureter (UBERON:0000056), bladder (UBERON:0001255, source), bloodstream (bacteremia/urosepsis). Long-term secondary organ: systemic (sepsis), progression to CKD.
- **Body systems:** Renal/urinary system (primary); cardiovascular/immune (sepsis); reproductive/obstetric (pregnancy-associated).
- **Tissues/cells:** Tubular and collecting-duct **epithelial cells** (targets); infiltrating **neutrophils** (CL:0000775) and **macrophages** (CL:0000235). Tissue type: epithelial and tubulointerstitial.

- **Subcellular:** Bacterial engagement at the **apical plasma membrane** (GO:0016324) of tubular epithelium; intracellular bacterial communities; neutrophil **azurophil granules** and NADPH-oxidase-driven ROS; NET chromatin extrusion (extracellular region, GO:0005576).
- **Localization / laterality:** Often **unilateral** (single kidney/segment), can be **bilateral**; EPN commonly affects one kidney with contralateral involvement possible; acute lobar nephronia is focal/segmental.

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8. Temporal Development

- **Onset:** Acute to subacute (hours–days). Age of onset **bimodal** — infancy and reproductive-age adulthood, with elderly resurgence.
- **Progression/stages:** Uncomplicated APN → (if untreated/host-vulnerable) → acute lobar nephronia → renal/perinephric abscess → emphysematous pyelonephritis → urosepsis. Chronic sequela: post-pyelonephritic scarring → CKD.
- **Course/duration:** Typically **self-limited with antibiotics** over 7–14 days; **delay >72 h predicts permanent scarring** (PMID: 27748543). Recurrence is common in the presence of unresolved predisposing factors (obstruction, VUR, diabetes).
- **Critical intervention window:** Prompt antibiotics (ideally within hours to <72 h) and, when obstruction is present, **urgent decompression** (nephrostomy/stent). Early nephrectomy (≤24 h) improves survival in fulminant EPN (PMID: 42221797).

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9. Inheritance and Population

Epidemiology. In a 19-year Danish population-based cohort (66,937 APN episodes in 57,162 patients; ICD-10), the **incidence roughly doubled** over 2000–2018 (PMID: 38020186):

Group	2000 (per 100,000/yr)	2018 (per 100,000/yr)
Women	6.8	15.4
Men	2.7	4.5
Infant girls	7.4	64.8
Infant boys	17.1	52.5

Direct quote: "*the incidence increased from 6.8 … to 15.4 … in women and from 2.7 … to 4.5 … in men*" and "*Among infants, the rate rose from 7.4 … to 64.8 … in girls and from 17.1 … to 52.5 … in boys*" (PMID: 38020186). The rise was driven largely by young children and not explained by increasing CAKUT prevalence. In US surveillance, pyelonephritis accounted for **19.9%** of invasive *E. coli* infections; APN affects ~**250,000 US patients annually** (PMID: 41627814, PMID: 32849562).

Inheritance. Not a monogenic disorder — no Mendelian inheritance pattern, penetrance, anticipation, founder effect, or carrier frequency applies. Susceptibility is **multifactorial/polygenic**, mediated by innate-immunity variants (IRF3, IL-8/rs4073, CXCR1) plus anatomic/metabolic risk.

Demographics. Strong **female predominance** across ages; infant male predominance in the neonatal period (before shifting female). Diabetics and pregnant women are over-represented in severe forms. No specific ethnic founder distribution; ESBL/fluoroquinolone-resistant strains show geographic variation (higher ESBL in complicated cases and certain regions).

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10. Diagnostics

Laboratory tests. Urinalysis (pyuria, leukocyte esterase, nitrites, hematuria), **urine culture with ≥10^5 CFU/mL** and susceptibility testing (essential given resistance), blood cultures in severe/hospitalized cases, CBC (leukocytosis), CRP, and creatinine/eGFR. LOINC: urine culture (630-4); leukocyte esterase (5799-2); nitrite (5802-4).

Biomarkers. - **Procalcitonin (PCT):** correlates with acute parenchymal involvement on DMSA (8.81 vs 1.7 ng/mL in lesion vs no-lesion, p=0.01) and predicts scarring (cut-off ~1 ng/mL, AUC 0.74), though it cannot replace DMSA (PMID: 23481452, PMID: 19205751, PMID: 27329559). - **Urinary NGAL (LCN2):** meta-analysis (13 studies) — sensitivity 0.88 (95% CI 0.79–0.94),

specificity 0.86 (0.78–0.92) for UTI; for APN sensitivity 0.79, specificity 0.78 (PMID: 39423110). In 321 febrile children uNGAL outperformed CRP/WBC for UTI and APN (AUC 0.860 and 0.780) (PMID: 33091975). uNGAL and PCT are higher in children who later scar (PMID: 40742430).

Imaging. Reserved for complicated/atypical/non-responding cases: **renal ultrasound** (hydronephrosis, abscess), **contrast-enhanced CT** (reference for EPN — intrarenal gas; abscess; obstruction), and **DMSA (^{99m}Tc-dimercaptosuccinic acid) scintigraphy** — the **reference standard for parenchymal involvement and scarring** in children (PMID: 27748543, PMID: 16894326). In XGP, CT shows the "bear-paw" sign with staghorn calculus (PMID: 41323310).

Genetic / omics diagnostics. Not indicated for routine diagnosis (APN is not a monogenic disease). Research-level host-susceptibility genotyping (IRF3, IL-8 rs4073, CXCR1) and pathogen whole-genome sequencing (virulence/resistance profiling, e.g., ST131-H30Rx) are used in studies, not clinical care (PMID: 40926251).

Clinical criteria & differential diagnosis. Diagnosis is clinical (fever + flank pain + CVA tenderness) plus pyuria/bacteriuria and positive culture; IDSA criteria used for pregnancy studies. Differentials: cystitis (no systemic/CVA signs), nephrolithiasis/renal colic, PID/STIs (co-occur in sexually active women — evaluate for cervical motion tenderness) (PMID: 40360224), ovarian vein thrombophlebitis (postpartum fever) (PMID: 42402563), appendicitis, and, in mass-forming XGP, renal cell/squamous carcinoma (PMID: 33282610).

Screening. In pregnancy, **screen for ASB with urine culture** (see §13) (PMID: 39349024).

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11. Outcome / Prognosis

Mortality. Uncomplicated APN has low mortality with prompt therapy. Severe/complicated forms are dangerous: in critically ill EPN, **ICU mortality ~15%**, with higher SAPS II independently predicting 90-day mortality (HR 1.08/point, 95% CI 1.05–1.12) and **early nephrectomy associated with lower mortality (HR 0.18, 95% CI 0.04–0.90, p=0.037)** (PMID: 42221797). In purulent pyelonephritis meta-analysis, overall mortality ~5.8% (342/5912), rising to 20–30% with septic shock (PMID: 42417339). In invasive *E. coli* infection surveillance, 7.9% died (PMID: 41627814).

Morbidity / complications. Urosepsis/septic shock, renal and perinephric abscess, emphysematous pyelonephritis, pyonephrosis, acute kidney injury, and **permanent renal scarring** → hypertension and CKD progression. UTI requiring hospital admission accelerates

eGFR decline in CKD patients and is a potentially modifiable CKD-progression factor (PMID: 40022942). In pregnancy, APN is linked to preterm birth and low birth weight (PMID: 41274602, PMID: 41684314).

Prognostic factors. Delay to treatment >72 h (scarring), VUR presence/grade, diabetes, obstruction, septic shock, pre-existing CKD, thrombocytopenia, and dialysis need. **Prognostic biomarkers:** elevated PCT and uNGAL predict acute parenchymal lesions and later scarring (PMID: 27748543, PMID: 40742430).

12. Treatment

Pharmacotherapy (empirical then culture-directed).

Setting	Agents	NCIT (suggested)	Evidence
Uncomplicated APN (outpatient)	Fluoroquinolone (ciprofloxacin/levofloxacin); TMP-SMX if susceptible	Ciprofloxacin C376; Levofloxacin C1637	7 days non-inferior to 14 days (PMID: 22726802)
Hospitalized / febrile UTI	3rd-gen cephalosporin (ceftriaxone) IV ± aminoglycoside; oral step-down	Ceftriaxone C287	SPILF guidelines (PMID: 42314979)
Complicated / ESBL / resistant	Carbapenem; **ceftazidime-avibactam** (carbapenem-sparing); piperacillin-tazobactam	Ceftazidime-Avibactam C120207	Non-inferior to doripenem (PMID: 27313268)
Uncomplicated (oral, ESBL)	Pivmecillinam, fosfomycin, nitrofurantoin (lower-tract)	Nitrofurantoin C61854	(PMID: 42130306)
Pregnancy	Cephalosporins (cefixime), IV for pyelonephritis	—	(PMID: 39349024, PMID: 39563593)

Duration. Landmark RCT: **ciprofloxacin 500 mg BID × 7 days is clinically and bacteriologically non-inferior to 14 days** in women with community-acquired APN (248 randomized) (PMID: 22726802). In children, ≤7-day and oral courses may not increase recurrence versus longer/parenteral therapy (PMID: 42803594).

Resistance context. Empirical therapy is constrained by resistance: fluoroquinolone resistance **6.3% (uncomplicated) vs 19.9% (complicated)** and ESBL production **2.6% vs 12.2%**, with **34.5% of ESBL cases community-acquired** and most ESBL/FQ-resistant cases initially treated with inactive drugs (PMID: 27532362). ST131-H30Rx ESBL clones drive recurrence (PMID: 40926251).

Surgical / interventional. Urgent **decompression** (percutaneous nephrostomy or ureteral stent) for obstruction; **percutaneous drainage** for abscesses >3–5 cm (avoids open surgery in 80–90%); **nephrectomy** for fulminant EPN/XGP; XGP may sometimes be managed with kidney-preserving therapy in non-septic patients (PMID: 42417339, PMID: 26889137).

Supportive care. IV fluids, antipyretics/analgesia, vasopressors and ICU care for septic shock; glycemic control in diabetics.

Experimental / precision approaches. FimH mannoside inhibitors (e.g., FIM1033) attenuate bacterial loads in pyelonephritis models — an anti-adhesion, non-antibiotic strategy (PMID: 33513212).

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13. Prevention

Primary prevention. - **Pregnancy screen-and-treat of ASB** — cornerstone: "*During pregnancy, there is increased risk of ascending urinary tract infection (UTI) resulting in pyelonephritis and associated preterm delivery and low birth weight*" (PMID: 41274602); "*Screening for ASB with a urine culture is required during pregnancy, and a positive culture is treated for 5 to 7 days with culture-specific antibiotics*" (PMID: 39349024). ASB is common (e.g., 29% culture-positive, 72% asymptomatic in a tertiary cohort) (PMID: 42516470); risk-factor-based selective screening is emerging to balance stewardship (PMID: 41274602). - Hydration, voiding hygiene, glycemic control, and source control of stones/obstruction.

Recurrence prevention (non-antibiotic, RCT-supported). - **Sublingual vaccine MV140** — "*Immunoprophylaxis with the sublingual vaccine MV140 significantly reduced recurrence compared with placebo, with 56–58% of women remaining UTI free in a large RCT*" (PMID: 42133003). - **Methenamine hippurate** — "*non-inferior to daily antibiotic prophylaxis in preventing rUTIs*" (PMID: 42133003); supported alongside cranberry and (postmenopausal) vaginal estrogen in an overview of 27 systematic reviews, while probiotics/D-mannose/vaccines need stronger evidence (PMID: 42225392). - **Vaginal estrogen** in postmenopausal women.

Antibiotic prophylaxis in VUR (children). The **RIVUR RCT** (>600 children) showed long-term antimicrobial prophylaxis **reduced UTI recurrence by 50%** (overall NNT ~10) (PMID: 35928985, PMID: 38244067). Re-analysis identified high-benefit subgroups (NNT ≤5): grade IV VUR and children with bladder-bowel dysfunction, especially with febrile index UTI (PMID: 37693511).

Secondary/tertiary prevention. Prompt treatment (<72 h) to prevent scarring; DMSA/imaging follow-up; management of obstruction/diabetes to prevent EPN and CKD progression.

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14. Other Species / Natural Disease

- **Taxonomy affected:** Humans (NCBI:txid9606) primarily; naturally occurring ascending bacterial pyelonephritis also affects companion animals — **dogs** (*Canis lupus familiaris*, txid9615) and **cats** (*Felis catus*, txid9685) — and livestock (cattle, pigs), typically from ascending *E. coli*/*Proteus*/*Enterococcus* UTIs, obstruction, or stones.
- **Comparative pathology:** Mechanisms are conserved — ascending uropathogen infection, obstruction/stasis predisposition, and neutrophil-mediated parenchymal injury. Veterinary relevance is significant in small-animal medicine (pyelonephritis as a cause of renal failure).
- **Orthologous host genes (NCBI Gene):** mouse *Irf3* (54131), *Tlr4* (21898; human *TLR4* 7099), functional chemokine homologs (mouse *Cxcl1/2* for human *CXCL8* 3576), *Cxcr1*, and *Dsg2* (mouse 13511; human *DSG2* 1829).
- **Transmission / zoonosis:** UPEC strains overlap between humans and animals/food (foodborne extraintestinal *E. coli* reservoirs), but APN itself is not classically person-to-person transmissible.

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15. Model Organisms

- **Mouse (murine) ascending UTI/pyelonephritis models** are the workhorse: transurethral UPEC inoculation in **C3H/HeN** and related strains reproduces ascending kidney infection, abscesses, and scarring.
- **Genetic models:** *Irf3*$^{-/-}$ mice show "*a pathogen-specific increase in acute mortality, bacterial burden, abscess formation and renal damage compared to wild type mice*," directly modeling

the human IRF3 susceptibility axis (PMID: 20886096). CXCR1/IL-8-axis and TLR4 models recapitulate the ASB-vs-pyelonephritis dichotomy (PMID: 11817650).

- **Mechanistic/receptor models:** FimH$^-$ UPEC mutants fail to colonize the kidney; DSG2 identified as the renal FimH receptor via CRISPR screen in collecting-duct cells; mannoside FIM1033 attenuates loads — establishing druggable anti-adhesion targets (PMID: 33513212).
- **Scarring/sex-difference models:** androgen-influenced activin-A macrophage polarization drives post-pyelonephritic scarring; sex differences in kidney bacterial community dynamics are modeled in mice (PMID: 32849562, PMID: 33468577).
- **In vitro / cellular:** Renal collecting-duct epithelial cell lines and CRISPR screens (FimH–DSG2 receptor identification); primary neutrophil functional assays (NET formation, ROS).
- **Phenotype recapitulation & limitations:** Mouse models faithfully reproduce ascension, neutrophil-dependent clearance, abscess/scarring, and adhesin dependence. Limitations: interspecies differences in chemokine biology (mice lack a direct IL-8/CXCL8 ortholog; functional homologs used), urinary-tract anatomy, and the human polymorphism spectrum; EPN (diabetes-driven, gas-forming) is less commonly modeled.
- **Resources:** MGI (mouse), plus UPEC strain collections; models used to study innate immunity, virulence, scarring, and anti-adhesion/vaccine therapeutics.

Mechanistic Model / Interpretation

```
UPEC colonization (introitus -> bladder)
             |  FimH->DSG2 ; P-fimbriae->glycosphingolipid   [PMID 33513212]
             v
Ascension to renal pelvis / collecting duct
             |  LPS/adhesins -> TLR4
             v
Epithelial innate sensing -> IRF3 + NF-kB -> IL-8 (CXCL8)    [PMID 20886096, 21042230]
             |  IL-8 -> CXCR1 on neutrophils
             v
NEUTROPHIL RECRUITMENT (decisive effector)                    [PMID 11817650]
       |------------- Branch A: robust axis --------------|
       |  phagocytosis, ROS, NETs -> clearance             |-> ASB / resolution  [PMID 39321268]
       |                                                   |
       |------------- Branch B: weak axis ----------------|
          (low CXCR1; IRF3/IL-8 rs4073 risk genotype)     |-> ACUTE PYELONEPHRITIS
             |  parenchymal proliferation, abscess        |
             v                                             |
  Dysregulated neutrophil injury (ROS, proteases,          |
  S100A8/A9, NETs) + androgen-macrophage activin-A         |-> RENAL SCARRING -> HTN/CKD
             |                                       [PMID 42524556, 32849562, 40022942]
             v
  Branch C (diabetes/obstruction): gas-forming necrosis    -> EMPHYSEMATOUS PN -> SEPSIS/DEATH
                                                            [PMID 42221797]
```

The unifying theme is that **APN is a disease of the host–pathogen interface**: an identical UPEC exposure yields divergent outcomes (silent carriage vs destructive parenchymal infection vs necrotizing sepsis) depending on host innate-signaling genotype, anatomy (VUR/obstruction), and metabolic state (diabetes/pregnancy). This explains why therapy is not only antimicrobial but also directed at **source control** (decompression, drainage, nephrectomy) and why prevention targets the **modifiable environmental inputs** (ASB in pregnancy, obstruction, recurrence). Neutrophils are the pivotal, double-edged effector — indispensable for clearance yet responsible for the scarring that links acute infection to chronic kidney disease.

Evidence Base

PMID	Contribution	Type
20886096	IRF3-dependent innate resistance; human promoter polymorphism → symptomatic kidney infection	Mouse + human genetics
11817650	Neutrophils as critical effectors; CXCR1/IL-8 dysfunction → pyelonephritis + scarring	Review/ mechanism
21042230	IL-8 rs4073 associates with pediatric parenchymal renal infection	Human genetics
33513212	DSG2 as renal FimH receptor; FimH mannoside FIM1033 therapy	Mouse + in vitro
39321268	Urinary NETs protect against ascension; basis of leukocyte dipstick	Human + mouse
42524556	Neutrophil double-edged role; effector molecules of injury/fibrosis	Review
32849562	Androgen–activin-A macrophage polarization → scarring; ~250k US cases/yr	Mouse
27532362	US resistance rates (FQ, ESBL) in APN; *E. coli* 86.9%	Prospective cohort
42221797	EPN ICU cohort; diabetes/shock/obstruction; early nephrectomy benefit	Multicenter cohort
38020186	Population incidence doubling; sex/infant distribution	Registry cohort
22726802	7 vs 14 day ciprofloxacin non-inferiority	RCT
27313268	Ceftazidime-avibactam vs doripenem for complicated UTI/APN	Phase 3 RCT
42133003	MV140 vaccine, methenamine non-inferiority	Systematic review
42225392	Overview of 27 SRs on non-antibiotic prevention	Overview of SRs
35928985 / 37693511	RIVUR: 50% recurrence reduction; high-benefit subgroups	RCT + re-analysis
27748543	Delay >72 h → scarring; DMSA outcomes	Pediatric cohort
	uNGAL diagnostic accuracy; predicts scarring	

PMID	Contribution	Type
39423110 / 33091975 / 40742430		Meta-analyses/ cohort
41274602 / 39349024	Pregnancy ASB screen-and-treat	Reviews
40022942	UTI/hospital admission accelerates CKD progression	Multicenter observational

Consistency/conflict. Findings are broadly consistent. One tension: procalcitonin's diagnostic value for parenchymal involvement varies by cut-off and study (PMID: 16894326 reported limited specificity), and a single-country pregnancy comparison found no difference in pyelonephritis rates between screening vs non-screening centers (PMID: 37515907), tempering the universality of screen-and-treat and supporting emerging **selective** screening.

Limitations and Knowledge Gaps

1. **No monogenic basis / modest host-genetics evidence.** Susceptibility variants (IRF3, IL-8 rs4073, CXCR1) derive from candidate-gene and small cohort studies; no large GWAS for APN susceptibility is established, and effect sizes/penetrance are not quantified for clinical use.
2. **Mechanistic reliance on mouse models.** Key adhesin (FimH–DSG2), IRF3, and scarring mechanisms are demonstrated primarily in mice; interspecies chemokine differences (no direct murine IL-8 ortholog) limit translation. Human FimH-mannoside efficacy is not yet clinically proven.
3. **Biomarker thresholds unstandardized.** uNGAL and PCT show promising accuracy but variable cut-offs; neither replaces DMSA. Prospective validation and standardized assays are needed.
4. **Prevention evidence heterogeneity.** ASB screening benefit rests partly on older/low-quality evidence; MV140 and methenamine are promising but need broader confirmation; RIVUR benefit is concentrated in specific subgroups with attendant resistance costs.

5. **Resistance evolution.** Community ESBL/fluoroquinolone-resistant *E. coli* (ST131-H30Rx) is rising, and much of the resistance/epidemiology data is regional (US, Danish, European), limiting global generalizability.
6. **Scarring→CKD causality.** The link between APN and CKD progression is largely observational and confounded by baseline renal function.

Proposed Follow-up Experiments / Actions

1. **Host-genetics validation:** Large multi-ancestry GWAS/targeted sequencing of APN-vs-ASB cohorts to confirm and quantify IRF3, *CXCL8* rs4073, CXCR1, and TLR4 effects; test as a clinical risk-stratification panel.
2. **Anti-adhesion translation:** Advance FimH mannoside inhibitors (FIM1033-class) into human trials for prevention/treatment of recurrent pyelonephritis, and evaluate DSG2-targeting strategies.
3. **Biomarker standardization:** Prospective, multicenter study to establish uNGAL/PCT cut-offs for APN diagnosis and scarring prediction, benchmarked against DMSA, to reduce unnecessary imaging.
4. **Precision prevention trials:** Head-to-head and combination RCTs of MV140, methenamine, and vaginal estrogen vs antibiotic prophylaxis, with resistance and adherence endpoints; define risk-factor-based selective ASB screening in pregnancy.
5. **Stewardship-driven treatment:** Broaden evidence for short-course and carbapenem-sparing regimens (ceftazidime-avibactam and newer β-lactam/β-lactamase inhibitors) in ESBL APN; embed rapid resistance diagnostics to reduce inactive empirical therapy (currently 45–76% in resistant cases).
6. **Scarring/CKD mechanism:** Test whether modulating the neutrophil injury arm (ROS, NETs, S100A8/A9) or androgen–activin-A macrophage axis prevents post-pyelonephritic fibrosis without impairing clearance; longitudinal cohorts to establish APN→CKD causality.

Report compiled from 13 confirmed findings across 69 reviewed papers over 5 iterations. Evidence spans human clinical cohorts/RCTs, population registries, systematic reviews/meta-analyses, mouse models, and in-vitro mechanistic studies, with source types indicated throughout.