Pneumonia Caused By *Pseudomonas aeruginosa* Infection — Comprehensive Disease Report

Target disease: Pneumonia Caused By *Pseudomonas aeruginosa* Infection **MONDO ID:** MONDO:0037398 · **Category:** Infectious Disease **Pathogen taxon:** *Pseudomonas aeruginosa* — NCBI:txid287 (species); genus *Pseudomonas* NCBI:txid286 **Investigation:** 5 iterations · 9 confirmed findings · 61 papers reviewed · Report date 2026-09-30

Summary

Pneumonia caused by *Pseudomonas aeruginosa* is an **opportunistic Gram-negative lower-respiratory-tract infection** that predominantly afflicts hosts with compromised mechanical or immune barriers — mechanically ventilated ICU patients, neutropenic and immunocompromised patients, and people with structural lung disease such as cystic fibrosis (CF) and bronchiectasis. It is not a heritable Mendelian disorder; its "etiology" is infectious, with host genetics (most paradigmatically *CFTR* mutations) acting as susceptibility modifiers rather than causes. Clinically it is one of the leading causes of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), and it is increasingly **multidrug-resistant (MDR)** and **carbapenem-resistant (CRPA)** — a WHO critical-priority pathogen.

The pathophysiology splits into two mechanistic branches. In **acute pneumonia**, the **Type III Secretion System (T3SS)** injects cytotoxic effectors (ExoU, ExoS, ExoT, ExoY) into host cells, while flagellin is sensed by **TLR5** on airway epithelium and the T3SS is sensed by the **NLRC4 inflammasome** in alveolar macrophages, driving IL-1β-mediated neutrophilic inflammation, alveolar–capillary barrier destruction, acute lung injury/ARDS and, frequently, death. In **chronic pneumonia** (the CF/bronchiectasis paradigm), conversion to a **mucoid, alginate-overproducing biofilm phenotype** evades opsonic and non-opsonic phagocytosis and establishes lifelong airway persistence with progressive lung-function decline.

Prognosis is dominated by two modifiable factors — **antimicrobial resistance** and **inappropriate initial empiric therapy** — both of which sharply raise mortality. VAP attributable mortality is roughly 30%, and 28-day all-cause mortality in ventilated HAP/VAP trials remains ~20–26%. First-line management uses anti-pseudomonal β-lactams; **ceftolozane/tazobactam** was non-inferior to meropenem in the phase 3 ASPECT-NP trial. Prevention rests on ventilator-care bundles (with several traditional components now questioned), and emerging therapies include inhaled antibiotics, anti-virulence monoclonal antibodies, DNA vaccines, and bacteriophage therapy.

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1. Disease Information

Overview. *Pseudomonas aeruginosa* pneumonia is a lung parenchymal infection caused by the ubiquitous, aerobic, non-fermenting Gram-negative bacillus *P. aeruginosa*. It occurs mainly as **hospital-acquired pneumonia (HAP)** and **ventilator-associated pneumonia (VAP)**, and as chronic airway infection in structural lung disease. Acute *P. aeruginosa* pneumonia predominantly affects immunocompromised, neutropenic, and mechanically ventilated patients (PMID: 25520826, PMID: 9570172).

Key identifiers. - **MONDO:** MONDO:0037398 - **Causative organism — NCBI Taxonomy:** *Pseudomonas aeruginosa*, txid287 - **ICD-10:** J15.1 (Pneumonia due to *Pseudomonas*); **ICD-11:** bacterial pneumonia with *Pseudomonas* as the causal agent - **MeSH:** "Pneumonia, Bacterial" + "Pseudomonas Infections" / "Pseudomonas aeruginosa" - **OMIM/Orphanet:** Not applicable as a Mendelian entity (infectious disease); *CFTR*/cystic fibrosis (OMIM 219700; Orphanet ORPHA:586) is the relevant host-susceptibility entry.

Synonyms / alternative names. *Pseudomonas* pneumonia; *Pseudomonal* pneumonia; *P. aeruginosa* lower respiratory tract infection; *Pseudomonas aeruginosa* HAP/VAP; nosocomial *Pseudomonas* pneumonia.

Data source type. This report aggregates **disease-level resources** (surveillance cohorts, randomized trials, mechanistic model-organism and in-vitro studies, and registry data) rather than individual EHR-derived patient records.

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2. Etiology

Primary cause (infectious). The disease is caused by infection with *P. aeruginosa*. It is fundamentally an **opportunistic** infection: host predisposition defines who develops disease.

Risk factors (environmental / host). - **Mechanical ventilation / endotracheal intubation** — the dominant risk setting; VAP incidence is ~7–15% of ventilated patients (PMID: 30390751), and prolonged ventilation, reintubation and elevated CRP associate with VAP (PMID: 42592972). - **Immunocompromise / neutropenia** — *P. aeruginosa* was the most frequent organism in bacteremic pneumonia in neutropenic cancer patients (PMID: 9570172). - **Structural lung disease** — cystic fibrosis and bronchiectasis (chronic branch). - **Prior antibiotic exposure** — drives resistant strains and inappropriate initial therapy; associated with higher mortality (51.3% vs 34.0%, p<0.001) in Gram-negative severe sepsis (PMID: 21499086). - **Comorbidities** — diabetes (independently associated with MDR infection, adjusted OR 2.82), cardiovascular disease, COPD, hypertension (PMID: 42393552); ECMO support (PMID: 42685911); chest trauma with high injury-severity score and tracheostomy (PMID: 41978407).

Genetic (host susceptibility) risk factors. - **CFTR mutations (cystic fibrosis).** The paradigmatic host genetic risk factor for *chronic* pulmonary *P. aeruginosa* infection. CF produces progressive lung disease with chronic infection, mucus accumulation, airway inflammation and structural damage, with *P. aeruginosa* as a dominant chronic pathogen (PMID: 38702073, PMID: 41010996). The most common allele is **F508del** (PMID: 38742380). - **Inflammasome variants.** Gain-of-function variants in **NLRP3/NLRC4** inflammasome genes have been associated with clinical outcomes in CF (PMID: 33848452).

Protective factors. No validated protective genetic variant is established for this infectious disease. Environmental/behavioral protection is essentially **prevention of acquisition** (see §13): avoiding intubation, minimizing sedation, early extubation and mobilization (PMID: 31585480). Innate effectors such as **Cmpk2** enhance neutrophil phagocytosis and host survival (model-organism evidence; PMID: 40616692).

Gene–environment interactions. The clearest interaction is *CFTR* deficiency × environmental *P. aeruginosa* exposure → chronic mucoid airway infection. Prior-antibiotic environment × bacterial resistance genotype → inappropriate therapy → death is a second, treatment-relevant interaction.

3. Phenotypes

P. aeruginosa pneumonia presents as a bacterial pneumonia syndrome; phenotypes are acquired clinical manifestations, not congenital.

Phenotype	Type	Onset	Severity / course	Frequency	Suggested HPO
Fever	Clinical sign	Adult-onset (acquired)	Variable	Common	HP:0001945
Cough / productive cough	Symptom	Acquired	Variable	Common	HP:0012735
Dyspnea	Symptom	Acquired, acute/ subacute	Moderate–severe	Common	HP:0002094
Hypoxemia / respiratory failure	Lab/ physiologic	Acute	Severe	Frequent in ICU	HP:0012418 / HP:0002878
Purulent sputum / tracheal secretions	Sign	Acquired	Variable	Common (VAP)	HP:0025440
Leukocytosis	Lab abnormality	Acute	Variable	Common	HP:0001974
Elevated CRP	Lab abnormality	Acute	Marker of burden (AUC 0.83 for VAP)	Common (PMID: 42592972)	HP:0011227
Bacteremia / sepsis / septic shock	Complication	Acute	Severe, high-mortality	Subset (poor outcome)	HP:0031273 / HP:0100806
Pulmonary infiltrates / consolidation	Imaging sign	Acute	Variable	Diagnostic	HP:0031977
ARDS / acute lung injury	Physiologic	Acute	Severe	T3SS-driven subset	HP:0033677

Quality-of-life impact. Acute *P. aeruginosa* pneumonia in ventilated patients prolongs mechanical ventilation (12.5 vs 7.3 days) and hospitalization (19.6 vs 12.2 days) (PMID: 42592972). In the chronic CF branch, persistent infection drives progressive lung-function decline, exacerbations, and reduced survival (PMID: 38702073).

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4. Genetic / Molecular Information

No human causal gene produces *P. aeruginosa* pneumonia — it is infectious. Genetics operates on two axes:

(a) Host susceptibility / modifier genes (human). - **CFTR** (HGNC:1884; OMIM 602421) — loss-of-function mutations (F508del most common) cause CF and predispose to chronic *P. aeruginosa* airway infection (PMID: 38742380, PMID: 42774065). Variant classes include in-frame deletion (F508del), nonsense/stop-codon, splice, and gating variants; population-specific alleles (e.g., N1303K, G542X, 2789+5G>A enriched in Italy) exist (PMID: 42370441). - **NLRP3 / NLRC4** — inflammasome gain-of-function variants associated with CF outcomes (PMID: 33848452). - **TLR5, MUC1** — innate-sensing genes that modulate epithelial responses (PMID: 16239509, PMID: 22250084).

(b) Bacterial virulence & resistance loci (pathogen genome). - **T3SS effector genes:** *exoU* (phospholipase A2, most cytotoxic), *exoS* (ADP-ribosyltransferase + GAP), *exoT* (GAP), *exoY* (nucleotidyl cyclase); master regulator *exsA* (PMID: 25520826, PMID: 15972518). - **Alginate biosynthesis:** *algD* operon, regulator *mucA* (mucoid conversion) (PMID: 37009499). - **Flagellin:** *fliC* (TLR5 ligand) (PMID: 16239509). - **Resistance determinants:** carbapenemase and other AMR genes confirmed by whole-genome sequencing in high-risk clones (PMID: 41751514).

Epigenetics / chromosomal abnormalities: Not applicable to the disease as an infectious entity in humans.

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5. Environmental Information

Infectious agent. *Pseudomonas aeruginosa* (NCBI txid287), an aerobic, motile, non-fermenting Gram-negative bacillus. It is environmentally ubiquitous (water, moist surfaces, hospital reservoirs, medical devices) and forms biofilms on ventilator circuits and endotracheal tubes.

Environmental / occupational factors. Hospital and ICU environments, contaminated respiratory equipment, and indwelling devices are the principal reservoirs; >90% of MDR carbapenem-resistant *P. aeruginosa* isolates in one large UAE survey originated in hospitals (PMID: 41826861).

Lifestyle factors. Not the primary drivers; smoking/COPD contribute to structural lung disease that raises susceptibility (PMID: 42393552).

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6. Mechanism / Pathophysiology

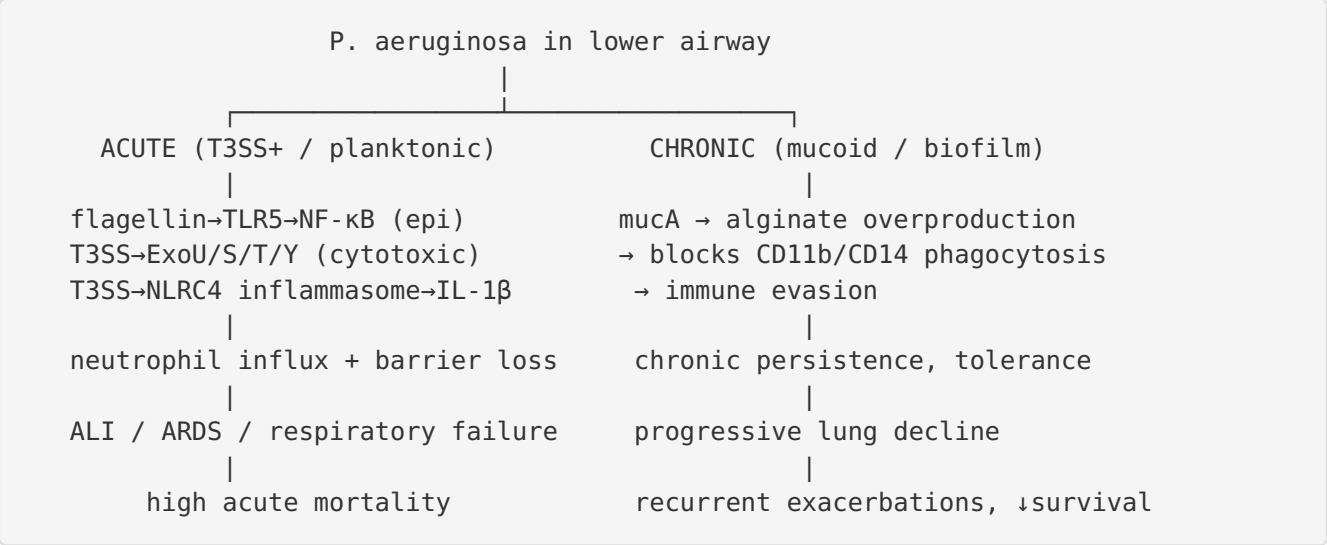
Ordered causal chain

ACUTE CYTOTOXIC BRANCH (ventilated / immunocompromised host):

1. *P. aeruginosa* colonizes the lower airway (aided by ventilation, impaired clearance) → **leads to** contact with alveolar epithelium and macrophages.
2. Bacterial **flagellin** is recognized by **TLR5** on the apical surface of airway epithelial cells → **results in** NF-κB activation and pro-inflammatory chemokine/cytokine transcription (PMID: 16239509). *(MUC1 tethers to TLR5 and dampens this signal — a counter-regulatory branch; PMID: 22250084.)*
3. The **Type III Secretion System** injects effectors **ExoU/ExoS/ExoT/ExoY** into host cells → **causes** direct cytotoxicity; ExoU (phospholipase A2) is most cytotoxic and **induces mitochondrial damage** in macrophages (PMID: 35130452).
4. Alveolar macrophages **detect the T3SS → activate the NLRC4 inflammasome** → caspase-1 → **IL-1β/IL-1α release** (PMID: 42779855). NLRC4 activation also **attenuates macrophage phagocytosis**, worsening bacterial persistence (inferred causal link from model organism; PMID: 33489931).
5. IL-1β-driven inflammation → **massive neutrophil recruitment** and alveolar–capillary barrier disruption → **increased permeability, pulmonary edema, protein-rich BALF** (demonstrated as ↑wet/dry ratio and ↑BALF protein in the T3SS-competent CHA strain vs *exsA*-null mutant) (PMID: 15972518).
6. → **Acute lung injury / ARDS, hypoxemic respiratory failure, sepsis/septic shock** → death in a substantial fraction.

CHRONIC PERSISTENCE BRANCH (CF / bronchiectasis host):

1. Impaired mucociliary clearance (e.g., *CFTR* loss) → chronic airway colonization.
2. *mucA* mutation → **alginate overproduction** → conversion to **mucoid biofilm** phenotype.
3. Alginate **inhibits opsonic and non-opsonic phagocytosis** by human (THP-1) and murine (MH-S) macrophages, blocking CD11b/CD14 receptor–ligand interactions (PMID: 37009499).
4. → **immune evasion, chronic persistent infection, antibiotic tolerance** → recurrent exacerbations, progressive lung-function decline, mortality (PMID: 38702073).



Cell types & GO/CL terms. Alveolar epithelial cells (CL:0000066; type II CL:0002063), **alveolar macrophages** (CL:0000583), **neutrophils** (CL:0000775). Biological processes: T3SS-dependent cytotoxicity, **inflammasome complex assembly (GO:0140738)**, **NLRC4 inflammasome activation**, **IL-1β production (GO:0032611)**, **TLR5 signaling (GO:0034146)**, **neutrophil chemotaxis (GO:0030593)**, **phagocytosis (GO:0006909)**. Subcellular: **mitochondrion (GO:0005739)** (ExoU damage), plasma membrane, extracellular alginate matrix.

Molecular profiling. Multi-omics of acute *P. aeruginosa* infection and mitochondrial gene-expression analysis of ARDS datasets (GEO) identified Cmpk2 as an innate-immune protective node enriched in neutrophils by scRNA-seq (PMID: 40616692, PMID: 40216004).

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7. Anatomical Structures Affected

- **Primary organ:** Lung (UBERON:0002048), lung parenchyma / alveoli (**alveolus UBERON:0002299**), respiratory system (UBERON:0001004).

- **Secondary involvement:** Bloodstream (bacteremia/sepsis), systemic multi-organ dysfunction in septic shock; ARDS affects the alveolar–capillary unit bilaterally.
- **Tissues:** Airway and alveolar **epithelium** (apical surface where TLR5 is expressed on human tracheal epithelium; PMID: 16239509); pulmonary capillary endothelium; alveolar interstitium.
- **Cells (CL):** alveolar macrophages (CL:0000583), neutrophils (CL:0000775), alveolar type I/II epithelial cells (CL:0002062 / CL:0002063).
- **Subcellular (GO CC):** mitochondrion (GO:0005739), plasma membrane, cytosolic inflammasome.
- **Localization / lateralization:** Typically **bilateral** in VAP/ARDS; may be unilateral/multilobar in focal bronchopneumonia.

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8. Temporal Development

- **Onset (acute branch):** Acute to subacute, developing over hours–days; VAP is defined as pneumonia arising **>48 h after intubation**, with early-onset (~58%) and late-onset (~42%) forms (PMID: 41939663).
- **Onset (chronic branch):** Insidious, beginning in childhood in CF and progressing over decades (PMID: 38702073).
- **Progression:** Acute disease can progress rapidly to ARDS, septic shock and death; the chronic branch follows a relapsing–remitting course of exacerbations superimposed on progressive decline.
- **Duration:** Acute pneumonia is treated over days–weeks; chronic *P. aeruginosa* airway infection is typically lifelong once mucoid biofilm is established.
- **Remission:** Acute disease can resolve with appropriate, timely antimicrobial therapy; chronic mucoid infection rarely eradicates. **Critical intervention window:** early appropriate empiric therapy (see §11) is the key modifiable determinant of outcome.

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9. Inheritance and Population (Epidemiology)

Inheritance: Not applicable (infectious disease). Host susceptibility via *CFTR* is autosomal recessive.

Epidemiology (frequency as HAP/VAP pathogen).

Setting / cohort	*P. aeruginosa* rank / frequency	Resistance	PMID
Chinese HAP, 37 hospitals (n=543)	3rd, 13.73% (behind *A. baumannii* 24.89%, *K. pneumoniae* 21.57%); HAP mortality 15.8%	—	41758741
Egyptian ICU VAP (n=120)	47/120 (39.2%)	85.1% MDR; 80% colistin-S, only 12.5% CAZ/AVI-S	41877050
Saudi HA-GNB, 5-yr (n=377)	2nd, 34.0%	meropenem-R 34.3%; ciprofloxacin-R 44.4%	42393552
UAE MDR-CRO surveillance	MDR-CR *P. aeruginosa* period prevalence 12.9%	carbapenem-resistant	41826861
Bosnian ICU VAP (n=118)	2nd after *A. baumannii*; VAP 34.7%	Gram-neg ≈85%	42592972

Chronic CF branch: chronic *P. aeruginosa* infection affects ~30–37% of adults and ~5–7% of paediatric CF patients in the Italian CF Registry, declining with CFTR-modulator therapy (PMID: 38742380, PMID: 42370441).

Geographic distribution: Global; MDR/CRPA burden is rising, with regional variation and WHO critical-priority status (PMID: 42523687). **Sex/age:** Reflects the underlying ICU/comorbid population (older adults, male predominance in several cohorts).

10. Diagnostics

Clinical/lab tests. - **Microbiology (gold standard):** culture of respiratory specimens — endotracheal aspirate (ETA) or bronchoalveolar lavage (BAL), with semi-quantitative thresholds ($\geq 10^5$ CFU/mL for ETA) (PMID: 41939663, PMID: 42801252). Antimicrobial

susceptibility testing (CLSI) is essential given high MDR rates. - **Inflammatory markers / biomarkers:** CRP discriminates VAP (AUC 0.83; PMID: 42592972); leukocytosis; bronchoalveolar **IL-1β** correlates with bacterial burden and may mark ongoing/unresolved infection (PMID: 12626989). - **Molecular/genomic:** whole-genome sequencing profiles resistance and virulence (PMID: 41751514); metagenomic next-generation sequencing aids complex cases (PMID: 42661655). - **Imaging:** chest radiograph/CT showing infiltrates/ consolidation (used with clinical criteria).

Clinical criteria. Modified Clinical Pulmonary Infection Score (CPIS >6), CDC/NHSN surveillance definitions for HAP/VAP; VAP requires pneumonia >48 h post-intubation (PMID: 41939663, PMID: 42393552).

Differential diagnosis. Other Gram-negative HAP/VAP pathogens (*A. baumannii*, *K. pneumoniae*), *S. aureus* pneumonia, aspiration pneumonitis, ARDS of non-infectious cause, pulmonary aspergillosis in the immunocompromised.

Genetic testing. Not for the infection itself; **CFTR sequencing / sweat chloride testing** is indicated when chronic *P. aeruginosa* infection suggests undiagnosed CF (diagnostic delay causes irreversible damage; PMID: 42774065).

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11. Outcome / Prognosis

Mortality. - VAP attributable mortality ~**30%** (PMID: 18060758). - 28-day all-cause mortality in ventilated HAP/VAP (ASPECT-NP, Gram-negative pathogens): **20.1%** (ceftolozane/tazobactam) vs **25.8%** (meropenem) (PMID: 35022730); ~23.7–24.0% with severe respiratory failure (PMID: 36773112). - Overall HA-GNB in-hospital mortality up to ~40% in high-comorbidity cohorts (PMID: 42393552).

Dominant prognostic factors (modifiable). 1. **Carbapenem/multidrug resistance** — CR infections carry significantly higher mortality across pathogens including *P. aeruginosa* (multicentre Indian surveillance, 159,336 patients; PMID: 42707186). 2. **Inappropriate initial therapy** — prior-antibiotic exposure → inappropriate empiric therapy (45.4% vs 21.2%) → higher hospital mortality (51.3% vs 34.0%) (PMID: 21499086). 3. Shock/vasopressor use, severe organ failure (SOFA) (PMID: 36773112, PMID: 36457059).

Complications: bacteremia, septic shock, ARDS, multi-organ failure; prolonged ventilation and hospitalization; in CF, progressive respiratory failure and death (median age at death in Italian CF registry 43–57 years) (PMID: 38742380, PMID: 42370441).

12. Treatment

First-line pharmacotherapy — anti-pseudomonal β-lactams. - **Ceftolozane/tazobactam** (3 g q8h) — non-inferior to meropenem in the phase 3 double-blind **ASPECT-NP** trial (NCT02070757) for ventilated HABP/VABP; for Gram-negative pathogens 28-day ACM 20.1% vs 25.8%, clinical cure 60.6% vs 57.1%, microbiologic eradication 73.0% vs 67.9%; *P. aeruginosa* comprised 25.0% of baseline LRT pathogens (PMID: 35022730). Efficacy held across renal-clearance and organ-failure subgroups (PMID: 34600585, PMID: 36773112). *(NCIT: Ceftolozane-Tazobactam.)* - **Meropenem/carbapenems** — comparator standard (PMID: 35022730). *(NCIT: Meropenem.)* - Other anti-pseudomonal agents: piperacillin-tazobactam, cefepime, ceftazidime, ceftazidime-avibactam, aztreonam, fluoroquinolones, aminoglycosides (guided by susceptibility, given high resistance rates).

For carbapenem-resistant *P. aeruginosa* (CRPA). Indian ICU guidelines (GRADE) favor **non-polymyxin** regimens for CRPA where efficacy is comparable but polymyxin toxicity is higher (42.1% vs 17.9%) (PMID: 42523687). Colistin remains active against many MDR isolates (80% colistin-S in an Egyptian VAP series) (PMID: 41877050).

Adjunctive / inhaled therapy. High-dose inhaled colistin followed by inhaled amikacin/tobramycin plus systemic therapy achieved clinical improvement and microbiologic eradication in MDR *P. aeruginosa* HAP/VAP despite in-vitro resistance, via high intrapulmonary concentrations (PMID: 42807670, PMID: 18060758).

Experimental / advanced therapeutics. - **Anti-virulence monoclonal antibodies:** fully human antibody cocktail targeting PcrV (T3SS tip), exotoxin A, and PA0833 gave broad-spectrum protection (PMID: 42662857); complement-activating CoMiX targeting Psl improved survival in murine pneumonia (PMID: 40961506). - **Bacteriophage therapy:** inhaled phage case series showed clinical/microbiological improvement without major adverse events (PMID: 41887374); murine efficacy depends on synergy with neutrophils, and alveolar macrophages can limit phage density (PMID: 40595615).

Supportive care: mechanical ventilation, oxygenation, hemodynamic support for sepsis, source control (device management), antimicrobial stewardship.

13. Prevention

Primary prevention (avoid acquisition). Ventilator-care bundles are central. The **2026 SIAARTI consensus** endorsed **subglottic secretion drainage** and **endotracheal cuff-pressure control**; it did **not** recommend routine chlorhexidine oral care (outside cardiac surgery) and questioned selective digestive decontamination (SDD) (PMID: 42415225). Objectively beneficial measures include **avoiding intubation, minimizing sedation, spontaneous awakening/breathing trials, early extubation and mobilization**; oral chlorhexidine may increase mortality and stress-ulcer prophylaxis may facilitate pneumonia; SDD lowers VAP/mortality in low-resistance but not high-resistance ICUs (PMID: 31585480, PMID: 28759469, PMID: 32486132).

Secondary prevention. Early recognition/risk stratification (ISS, tracheostomy timing, CRP, ventilation duration) (PMID: 41978407); antimicrobial stewardship to preserve appropriate empiric therapy (PMID: 42393552).

Tertiary prevention. Infection control to prevent MDR spread (>90% of MDR-CRPA hospital-sourced; PMID: 41826861); CFTR-modulator therapy reduces chronic *P. aeruginosa* prevalence in CF (PMID: 42370441).

Immunization (experimental). No licensed vaccine. An **OprF/PcrV bivalent DNA vaccine** with hydrogel delivery reduced bacterial burden and improved survival in a murine pneumonia model (PMID: 38359491).

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14. Other Species / Natural Disease

- **Taxonomy of pathogen:** *Pseudomonas aeruginosa* (NCBI txid287); broad host range.
- **Cross-species susceptibility:** *P. aeruginosa* pneumonia and infection occur across mammals; it is an opportunistic veterinary pathogen. Experimental infection is established in **mice**, **rats**, and **zebrafish** (PMID: 15972518, PMID: 40616692).
- **Comparative mechanisms:** Innate sensing (TLR5, NLRC4 inflammasome) and T3SS-mediated cytotoxicity are conserved across mammalian hosts, enabling model-organism study.
- **Zoonotic potential:** Environmental/opportunistic rather than classically zoonotic.

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15. Model Organisms

Model	Type	Use / findings	PMID
Rat acute lung injury	Mammalian, in vivo	T3SS-competent CHA vs *exsA*-null CHA-D1: T3SS drives ↑wet/dry ratio, ↑BALF protein, ↑mortality	15972518
Mouse acute pneumonia (intratracheal)	Mammalian, in vivo	Cmpk2-KO exacerbates ALI; NLRC4 inflammasome pathology; ASC/MSC, phage, mAb, vaccine efficacy	40616692, 33489931, 38359491, 40961506
Murine bone-marrow-derived macrophages	In vitro/ex vivo	ExoU induces mitochondrial damage	35130452
Zebrafish embryo	Vertebrate	Bacterial burden/survival; Cmpk2/STING-dependent phagocytosis	40616692
Human cell lines (A549, THP-1, MH-S, HEK293-TLR5)	In vitro	T3SS cytotoxicity (LDH), TLR5 signaling, alginate anti-phagocytosis	15972518, 37009499, 16239509

Recapitulation & limitations: Mouse/rat models faithfully reproduce acute T3SS-driven neutrophilic lung injury and inflammasome biology and are the workhorse for therapeutic testing; they less faithfully capture chronic human mucoid biofilm persistence, the full MDR resistance landscape, and human comorbidity context. Phage-therapy models further reveal immune–phage feedback (macrophages reduce phage density) that complicates translation (PMID: 40595615).

Key Findings (with statistical evidence)

F001 — T3SS is the principal acute virulence determinant. In a rat ALI model, the T3SS-expressing CHA strain caused significantly greater lung injury (higher wet/dry ratio and BALF protein at 12 h), increased A549 cytotoxicity, decreased clearance and increased mortality vs the isogenic *exsA*-null mutant CHA-D1. Four effectors — ExoS, ExoT, ExoU, ExoY — are canonical (PMID: 15972518, PMID: 25520826). The T3SS *"is involved in lung injury, septic shock, and a poor patient outcome."*

F002 — Leading MDR HAP/VAP pathogen. 3rd-ranked HAP pathogen in a 37-hospital Chinese cohort (13.73%); 39.2% of ICU VAP with 85.1% MDR in an Egyptian series; 2nd-ranked (34.0%) in a Saudi HA-GNB cohort (PMID: 41758741, PMID: 41877050, PMID: 42393552).

F003 — Ceftolozane/tazobactam non-inferior; mortality ~20–26%. ASPECT-NP: Gram-negative 28-day ACM 20.1% vs 25.8% (C/T vs meropenem); *P. aeruginosa* 25.0% of pathogens (PMID: 35022730).

F004 — Mucoid alginate/biofilm mediates immune evasion. In mucoid FRD1 vs *algD* mutant, alginate inhibited opsonic and non-opsonic phagocytosis by human and murine macrophages (PMID: 37009499).

F005 — Prevention rests on modifiable bundles; some components questioned. SIAARTI 2026 endorsed subglottic drainage and cuff-pressure control, not routine chlorhexidine; VAP incidence ~7–15% (PMID: 42415225, PMID: 30390751).

F006 — Host predisposition defines risk; CFTR/CF is the chronic paradigm. (PMID: 38702073, PMID: 9570172, PMID: 35927044).

F007 — Resistance and inappropriate initial therapy dominate prognosis. CR infections carry higher mortality across pathogens (PMID: 42707186); inappropriate initial therapy → 51.3% vs 34.0% mortality (PMID: 21499086); attributable VAP mortality ~30% (PMID: 18060758).

F008 — Emerging adjunctive/experimental therapies. Inhaled antibiotics, anti-virulence mAbs (PcrV/ETA/PA0833), DNA vaccine (OprF/PcrV), and bacteriophage therapy (PMID: 42807670, PMID: 42662857, PMID: 38359491, PMID: 41887374).

F009 — Innate sensing via TLR5 and NLRC4 drives IL-1β neutrophilic injury. TLR5 recognizes flagellin (PMID: 16239509); alveolar macrophages detect T3SS → NLRC4 → IL-1β (PMID: 42779855); ExoU damages mitochondria (PMID: 35130452); NLRC4 activation attenuates phagocytosis and drives pulmonary damage (PMID: 33489931).

Mechanistic Model / Interpretation

The nine findings cohere into a **two-branch model** in which the *same* pathogen produces two clinically distinct diseases depending on host context and bacterial phenotype. The **acute branch** is a *cytotoxic + hyperinflammatory* process: T3SS injection (F001, F009) both directly kills epithelial/immune cells (ExoU phospholipase, mitochondrial damage) and triggers NLRC4-

inflammasome IL-1β release, while flagellin–TLR5 amplifies NF-κB signaling. The convergent output is neutrophil-driven destruction of the alveolar–capillary barrier → ARDS → death. This branch dominates the ICU/ventilated/neutropenic population (F002, F006).

The **chronic branch** is an *immune-evasion + persistence* process: mucoid conversion (mucA→alginate) shields the biofilm from phagocytosis (F004), producing lifelong infection in structurally abnormal airways (CF/bronchiectasis; F006). Here the host genome (CFTR) is the key permissive factor.

Superimposed on both branches is the **resistance/therapy axis** (F002, F003, F007): outcomes are governed less by intrinsic virulence than by whether the organism is MDR/CRPA and whether initial empiric therapy is appropriate. This reframes prognosis as substantially *modifiable* through stewardship, rapid diagnostics, and next-generation agents (F003, F008). Prevention (F005) closes the loop by reducing acquisition upstream of all mechanisms.

Evidence Base

Domain	Key papers (PMID)	Contribution
Virulence / T3SS	15972518, 25520826, 35130452	Establish T3SS effectors as drivers of acute lung injury and mitochondrial damage
Innate sensing	16239509, 42779855, 33489931, 22250084	TLR5/flagellin and NLRC4/IL-1β inflammatory axis; MUC1 counter-regulation
Chronic persistence	37009499, 38702073, 41010996, 42774065	Mucoid alginate/biofilm immune evasion; CF host context
Epidemiology / MDR	41758741, 41877050, 42393552, 41826861, 42523687	Rank, frequency and resistance burden
Treatment	35022730, 36773112, 36457059, 34600585, 42807670, 42523687	RCT efficacy (ASPECT-NP); inhaled/CRPA strategies
Prognosis	42707186, 21499086, 18060758	Resistance and inappropriate therapy raise mortality
Prevention	42415225, 31585480, 28759469, 30390751, 32486132	Bundle components, incidence
Emerging therapy	42662857, 40961506, 38359491, 41887374, 40595615, 40616692	mAbs, vaccine, phage, host-directed

Limitations and Knowledge Gaps

- **No dedicated dataset was analyzed;** this is a literature-synthesis report, so all statistics derive from published cohorts/trials, each with their own design limitations (single-center retrospective series, subgroup analyses, non-inferiority framing).
- **Attribution vs association:** *P. aeruginosa*-attributable mortality is hard to isolate from severe underlying illness; the ~30% VAP figure is not pathogen-specific.
- **Mechanistic data are largely model-organism/in-vitro** (rat, mouse, zebrafish, cell lines). Human causal validation of the TLR5→NLRC4→IL-1β chain is inferential.

- **Host genetics** beyond *CFTR* and inflammasome variants are poorly defined; no robust human GWAS for *P. aeruginosa* pneumonia susceptibility was identified.
- **Emerging therapies** (mAbs, phage, DNA vaccine) rest on preclinical/case-series evidence without phase 3 RCT confirmation.
- **Ontology mappings** (ICD, HPO, GO, CL, UBERON, NCIT) are expert-suggested here and should be curator-verified.

Proposed Follow-up Experiments / Actions

1. **Stratify prognosis by T3SS genotype (exoU vs exoS).** Prospectively test whether *exoU*$^{+}$ clinical isolates predict worse ARDS/mortality, linking F001 to human outcomes.
2. **Clinical validation of PcrV-targeted anti-virulence mAbs** in ventilated HABP/VABP RCTs, building on preclinical protection (PMID: 42662857).
3. **Controlled trials of inhaled adjunctive antibiotics** for MDR/CRPA VAP with pharmacokinetic/pharmacodynamic endpoints (PMID: 42807670).
4. **Phage–immune interaction studies** to define dosing that overcomes macrophage-mediated phage clearance (PMID: 40595615).
5. **Biomarker-guided stewardship** using CRP/IL-1β and rapid resistance genotyping to shorten time to appropriate therapy (addresses F007).
6. **Host-directed therapy** targeting the NLRC4 inflammasome / Cmpk2–STING axis to rebalance protective vs damaging inflammation (PMID: 33489931, PMID: 40616692).
7. **Advance OprF/PcrV vaccine** toward first-in-human trials in high-risk ICU/CF populations (PMID: 38359491).

Report compiled from 5 investigation iterations, 9 confirmed findings, and 61 reviewed papers. Evidence types span human clinical (surveillance cohorts, ASPECT-NP RCT), model organism (rat/mouse/zebrafish), in-vitro (A549/THP-1/MH-S/HEK293), and computational (multi-omics/GEO) sources.
