



REVIEW

## Pseudomonas aeruginosa: A Persistent Pathogen and Current Approaches to Treatment- Microbiology

### Pseudomonas aeruginosa: un patógeno persistente y enfoques actuales de tratamiento microbiológico

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#### ABSTRACT

*Pseudomonas aeruginosa* (*P. aeruginosa*) represents an important bacterial pathogen, mainly because it may infect immunocompromised hosts, hospital patients, and people with cystic fibrosis (CF). Antimicrobial resistance has risen due to monitoring nosocomial *P. aeruginosa* infections, with tendencies toward model drug and carbapenem resistance. Some of the mechanisms of antimicrobial resistance include the downregulation of outer membrane porins, -lactamases, and multidrug efflux pumps. Toxins that be secreted and can build BioFlim (BF) are examples of virulence mechanisms. Effective therapy of infection caused by *P. aeruginosa* requires early delivery of the appropriate antibiotic medications, source control measures, and, where possible, prevention. Antibacterial de-escalation is supposed to be considered within patients by a positive clinical response, particularly as antibacterial susceptibilities were identified. Less common antibacterials, including Colistin, may be needed to treat multidrug-resistant *P. aeruginosa*, although additional anti-pseudomonal antibacterials should become accessible soon.

**Keywords:** Pseudomonas Aeruginosa (*P. Aeruginosa*); Virulence Mechanisms; Nosocomial; Colistin; Cystic Fibrosis (CF).

#### RESUMEN

*Pseudomonas aeruginosa* (*P. aeruginosa*) representa un importante patógeno bacteriano, principalmente porque puede infectar a huéspedes inmunodeprimidos, pacientes hospitalizados y personas con fibrosis quística (FQ). La resistencia a los antimicrobianos ha aumentado debido a la vigilancia de las infecciones nosocomiales por *P. aeruginosa*, con tendencia a la resistencia a los fármacos modelo y a los carbapenemes. Algunos de los mecanismos de resistencia a los antimicrobianos incluyen la regulación a la baja de las porinas de la membrana externa, las -lactamasas y las bombas de eflujo de múltiples fármacos. Las toxinas que se secretan y pueden formar BioFlim (BF) son ejemplos de mecanismos de virulencia. La terapia eficaz de la infección causada por *P. aeruginosa* requiere la administración precoz de los antibióticos adecuados, medidas de control de la fuente y, cuando sea posible, prevención. Se supone que la desescalada antibacteriana debe considerarse en los pacientes por una respuesta clínica positiva, en particular cuando se identificaron susceptibilidades antibacterianas. Es posible que se necesiten antibacterianos menos comunes, incluida la Colistina, para tratar la *P. aeruginosa* multirresistente, aunque pronto se debería poder acceder a otros antibacterianos antipseudomónicos.

**Palabras clave:** Pseudomonas Aeruginosa (*P. Aeruginosa*); Mecanismos De Virulencia; Nosocomial; Colistina; Fibrosis Quística (FQ).

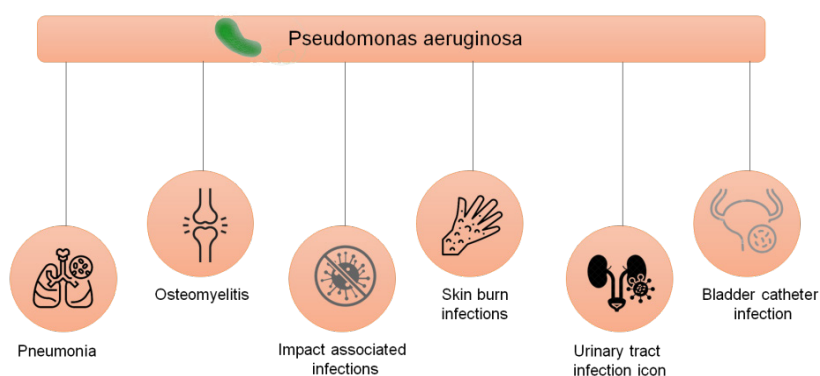
## INTRODUCTION

*P. aeruginosa* often causes infection cause within gram-negative bacteria, such as ventilator-associated wound infections, pneumonia, and Cystic Fibrosis (CF) lung infections, especially in severely ill and immunocompromised persons.<sup>(1)</sup> Especially in immunocompromised hosts, a *P. aeruginosa* infection considerably increases the cost of healthcare overall and may result in a severe, maybe deadly disease. Antibiotics are commonly used to treat *P. aeruginosa* bacteremia, although sometimes eradicating the infection may prove challenging and demand extended or extensive treatment.<sup>(2)</sup>

In nosocomial conditions, bacterial biofilm development must be avoided at all costs. Nosocomial infections caused by biofilm threaten human health and financial security since they may result in several potentially fatal illnesses. Scientists from all around the globe have developed a wide range of Metallic Nano-Particles (MNPs). At the same time, their effectiveness in treating bacterial infections, with those in strains opposing antibiotics, has been assessed. Most MNPS made of silver, copper, zinc, and gold can stop BioFilms (BF) from growing, but they have cytotoxic effects at high concentrations.<sup>(3)</sup>

In addition to soil, water, plants, human skin, and oral mucosa, *P. aeruginosa* is one of the most widely distributed and biochemically adaptable bacteria. For nutrition, it may also catabolize a broad range of chemical substances. The prevalence of infections rises as a result of *P. aeruginosa*'s capacity to flourish in a range of habitats, which raises its reservoirs and exposure hazards.<sup>(4)</sup>

The variety of virulence factors at the pathogen's disposal contributes to its adaptability and flexibility, enabling *P. aeruginosa* to tailor its response to various environmental cues. Understanding the pathoadaptability of this pathogen requires an understanding of the massive *P. aeruginosa* genome, which contains a variety of genetic regulatory mechanisms, particularly including novel genomic tools that allow the evaluation of differences and similarities among *P. aeruginosa* populations.<sup>(5)</sup> Schematic representations of the initial infections caused by *P. aeruginosa* are exposed in figure 1.



**Figure 1.** *Pseudomonas aeruginosa*'s primary infections

Hospital-acquired diseases are significantly challenged by heteroresistant infections linked to *P. aeruginosa*. However, more research must be done on the prevalence and effects of *P. aeruginosa* heteroresistance in clinical settings.<sup>(6)</sup>

Population genomics studies have shown various genetic differences in patients, including diverse lineages derived via patient-to-patient transmission for transmissible strains.<sup>(7)</sup> The study<sup>(8)</sup> offers information on the manufacture and control of this exopolysaccharide and reviews findings on the involvement of alginate in *P. aeruginosa*-induced CF-associated lung infections. *P. aeruginosa* isolates from 30 individuals with chronic diseases, and underlying non-CF respiratory illnesses were examined.<sup>(9)</sup>

The author<sup>(10)</sup> described a 17-month research of a group of MDR *P. aeruginosa* isolates that were taken as of an infantile feminine CF patient who has Double Lung Transplantation (DLP). The study<sup>(11)</sup> examined the growth of antibiotic resistance with antimicrobial tolerance in *P. aeruginosa* biofilms. The activity of Poly Morpho Nuclear leukocytes (PMNs) and the interaction between tobramycin and garlic have both been studied.<sup>(12)</sup>

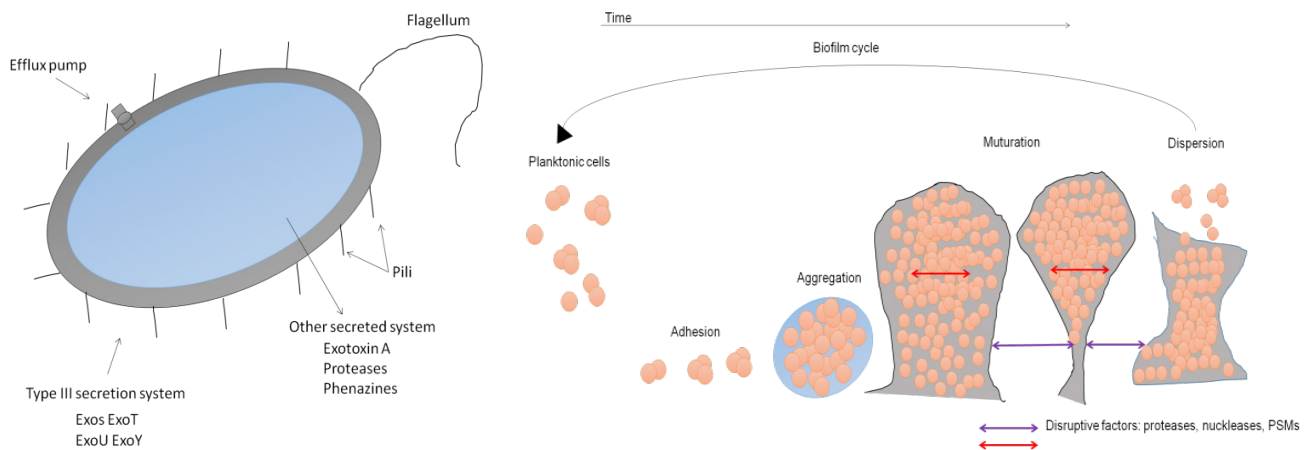
The study<sup>(13)</sup> focused on the strategy against bacterial biofilm development and quorum-sensing systems and evaluated the use of bacteriophages as a therapy. The research<sup>(14)</sup> was conducted because it was unknown if *P. aeruginosa* and subgingival periodontal pathogenic microorganisms in CF patients' lungs and oral cavities were related. The study<sup>(15)</sup> concentrated on the multiple benefits of phage treatment for *P. aeruginosa* biofilm reduction within medical plus in vitro studies to emphasize the therapy's broad applicability.

## DEVELOPMENT

### Virulence, infection, and resistance mechanisms

#### Attachment versus Motility

*P. aeruginosa* is motile and may facilitate first surface contacts thanks to its solitary flagellum. Numerous type IV cell surface pili, which are in charge of attachment to other surfaces and cell membranes, are also present in *P. aeruginosa*. Asia-Ganglioside M1 (aGM1), a glycolipid found on the surface of epithelial cells in the respiratory system, is one binding site. Only injured respiratory epithelium has been proven to harbor *P. aeruginosa*, which may be accounted for by the fact that aGM1 is mainly generated during the healing process of epithelial cells. Multiple pathogenic pathways may appear after cell surface attachment (figure 2).



**Figure 2.** (a) Mechanism of *P. aeruginosa* virulence as well as antibiotic resistance (b) Mode of BF growth

#### Quorum sensing, BF formation, and alginate secretion

The extracellular polysaccharide alginate is produced in excess by certain *P. aeruginosa* strains, a condition known as mucoid. Mutations in the *mucA* gene are common in mucoid isolates. AlgU, also known as AlgT<sub>22</sub>, may activate the genes responsible for producing alginate without MucA. Alginate may stop the sick host from eliminating microorganisms from its body by preventing phagocytosis, scavenging free radicals formed in macrophages, forming a substantial barrier to encourage neutrophil chemotaxis, activating complement along with preventing phagocytosis. Alginate also seems selected necessary for the development of *P. aeruginosa* Biofilms (BF).

A BF is a particular kind of bacterial growth that forms from the adhesion of microcolonies to a surface and their enclosing in a biopolymer matrix. *P. aeruginosa* BF has been seen within the airways of CF patients, and it is widely known that biofilms on indwelling medical devices may harbor bacteria.

#### Type 3 Secretion System (SS)

Type 3 SS may start to function after *P. aeruginosa* attaches to an epithelial cell. *P. aeruginosa* may directly inject certain effector protein molecules into epithelial cells via the such contact-dependent pathway, altering immune responses and causing cell damage and death. The four exoenzymes that have already been discovered, "ExoS, ExoT, ExoU, and ExoY", are articulated within dissimilar strains with contain a variety of roles.

Out of all the exoenzymes, ExoU may be the most harmful. Improved humanity in patients with "pneumonia, sepsis, respiratory failure, and more severe illness in Ventilator-Associated Pneumonia (VAP)" have all been linked to developing the type SS in *P. aeruginosa* isolates.

Type 3 SS was decreased in vivo *P. aeruginosa* pneumonia models in mice, rabbits, and rats by delivering antibody products that target PcrV. Compared to controls, this reduced lung damage, shock, and death.

#### Additional Secreted Virulence Elements

Although a comprehensive analysis is beyond the purview of this study, additional *P. aeruginosa* virulence factors are here briefly mentioned. For further detail, the reader is directed to two exceptional recent works. Eukaryotic elongation factor 2 is inhibited by exotoxin A, which prevents protein synthesis and kills host cells.

The surfactant proteins A, D, complement, antimicrobial peptides, and immunoglobulin are only a few examples of the host immunoregulatory proteins that secreted enzymes may break down. The host cells

are harmed by oxidative and pro-inflammatory processes caused by the released phenazines, which include pyocyanin, and affect the respiratory system.

### *Antimicrobial Resistance Mechanisms*

Antibacterial resistance often manifests as target structural modification, active efflux from the cell, enzymatic breakdown, and entrance blockage. *P. aeruginosa* may use any of these techniques to build resistance. The reason *P. aeruginosa* is intrinsically resistant to antibiotics is mostly due to the shallow permeability of its outer membrane compared to other Gram-negative bacteria like *Escherichia coli* and efflux mechanisms.

The multimodal efflux pumps of *P. aeruginosa* may lead it to export antibiotics. Effective efflux pump systems need to encompass the internal with external membranes between the membranes in the periplasm since they are thought of as tripartite geometries. The *P. aeruginosa* genome contains as a minimum ten separate efflux pump system operons, although only the multimodal efflux pumps "MexA-MexB-OprM," "MexC-MexD-OprJ," "MexE-MexF-OprN," and "MexX-MexY-OprM" have been thoroughly described.

The overexpression of a multimodal efflux pump that can handle a variety of antibacterial substrates increases the "Mean Inhibitory Concentration (MIC)" of any medication that is vulnerable to the efflux pump (table 1). The amount of pressure is applied by selecting strains of *P. aeruginosa* with excessive production of these efflux pumps. Due to these properties, fluoroquinolones that have been identified as the substrate of all four pumps for efflux listed above may provide unique challenges.

**Table 1.** Multidrug efflux pumps from *P. aeruginosa* with antibacterial substrates

MexX-MexY-OprM	MexA-MexB-OprM	MexE-MexF-OprN	MexC-MexD-OprJ
Sulbactam	Chloramphenicol	Levofloxacin	Gentamicin
Chloramphenicol	Aztreonam	Cefepime	Amikacin
Norfloxacin	Cefuroxime	Erythromycin	Erythromycin
Tetracycline	Faropenem		Faropenem
Ciprofloxacin	Carbenicillin	Cefuroxime	Cefepime
Clavulanic acid	Cefotaxime	Chloramphenicol	Cefotaxime
Levofloxacin	Ceftazidime	Ciprofloxacin	Ciprofloxacin
Norfloxacin	Clavulanic acid		Clavulanic acid
Norfloxacin	Cefuroxime	Erythromycin	Erythromycin
Trimethoprim	Ciprofloxacin	Nafcillin	Levofloxacin
MexE-MexF-OprN	MexA-MexB-OprM	MexC-MexD-OprJ	MexX-MexY-OprM

### **Therapy for *P. aeruginosa* infection**

#### *Procedures and Prevention Measures for Infection Control*

When possible, *P. aeruginosa* infections should be avoided to manage them. There are several accounts of nosocomially acquired *P. aeruginosa* infection outbreaks in the medical literature, and some cases may be linked to hospital staff members' chronic carriage conditions.

#### *Finding At-Risk Individuals and Gathering Cultural Data*

Healthcare-Associated Pneumonia (HCAP), Hospital-Acquired Pneumonia (HAP), or VAP, Intensive Care Units (ICU) contracting infections, neutropenic sepsis brought on by chemotherapy, acute leukemia, or AIDS, in addition to CF with rapidly increasing bronchiectasis, are some of the causes for using anti-pseudomonal antibacterial treatment. The fact that antibacterial regimens frequently undergo modification when an interfering bacterium is identified—ideally, before antibiotic treatment, if this can be done on time—highlights the need to acquire cultures.

#### *Source control with immediate antimicrobial treatment*

Antibacterial treatment shouldn't be deferred, especially in the highly ill, to deliver the proper antibacterials to the sickest patients—those with septic shock and severe sepsis within one hour. For the effective treatment of any ailment, source management is often necessary. Any early or persistent infections that may be treated with drainage, debridement, or removal should be thoroughly examined in patients.

After initial stabilization and the administration of antibiotics, abscesses with empyemas should be eliminated, contaminated surgical instruments should be removed, and additional sepsis causes should be treated with the support of qualified specialists.

### *The Advantages of Effective Initial Therapy*

It is well established that inappropriate initial empirical antibiotic dosing hurts patient outcomes. It was shown in a recent retrospective review that *P. aeruginosa* bloodstream infections needed the proper therapy. When sensitivity information was available, patients who did not get at least one drug that a bloodstream *P. aeruginosa* strain was sensitive to or whose first antibiotic treatment was insufficient had considerably higher mortality rates.

### *Treatment of P. aeruginosa: Combination vs Monotherapy*

Treatment for *P. aeruginosa* bacteremia was split into practical and conclusive approaches when it was shown that an appropriate scientific mixture Anti-Pseudomonal Therapy (APT) be linked utilizing decreased humanity in a single month than an acceptable empirical anti-pseudomonal monotherapy. There was no difference in the mortality rates between a good standard combination treatment and an excellent traditional monotherapy.

### *The theory of antibiotic de-escalation*

Treatment for *P. aeruginosa* bacteremia was split into empirical and definitive techniques when it was shown that a sufficient practical combination of APT was linked with reduced humanity in a single month than an acceptable experimental Anti-Pseudomonal Mono-Therapy (APMT). In addition, individuals with recurring infections and those who had previously had 15 days of antibiotic therapy are additional probable to multiresistant bacteria.

### *Recommendations for Specific Doses in P. aeruginosa*

Only sometimes are comparative trials of alternative dosage administration methods for the same antibacterial drug available. The pharmacokinetic/pharmacodynamic properties of the used antibacterial agents possess an impact on several recommendations for dosage administration. These characteristics vary amongst antimicrobial agent groups.

The “American Thoracic Society (ATS) with the Infectious Disease Society of America (IDSA)” has developed consensus recommendations for the treatment of nosocomial patients with late-onset pneumonia caused by a common bacterium, *P. aeruginosa*.

Table 2. The first empirical antibiotic therapy for <i>P. aeruginosa</i> pneumonia	
Antibacterial	Dosage
One of the following:	
Cefepime	IV1-2gevery8-12hours
Piperacillin/tazobactam	IV4,5gevery6hours
Imipenem cilastatin	IV500mgevery6hoursor1gevery8hours
Ceftazidime	IV2gevery8hours
Aztreonam	IV2gevery8hours
Meropenem	IV1gevery8hours
Plus one of the following:	
Gentamicin	IV7mg/kgoncedaily
Tobramycin	IV7mg/kgoncedaily

Table 2 lists acceptable anti-pseudomonal medications along with suggested dosages. Typically, therapy shouldn't go more than 7-8 days if there is a robust clinical response and standard lung architecture.

### **Alternatives to Antimicrobials**

#### *Colistin*

Due to the growing issue of MDR Gram-negative bacteria that might simply respond to these treatments whereas exhibiting a variety of resist techniques to exclude the employ of other drugs, the usage of colistin has grown lately. Intravenous Colistin's efficacy for treating severe infections caused by MDR bacteria is good, given that its use is sometimes necessary due to the absence of adequate substitutes. Due to the issue with MDR Gram-negative bacteria that might respond to this treatment even as demonstrating a range of resistance mechanisms that exclude alternate therapy, colistin usage has grown. Given that the lack of adequate alternatives often necessitates its use, intravenous Colistin seems effective in treating severe infections by MDR pathogens.



### Doripenem

“Doripenem is a brand-new 1-methyl-carbapenem” which is stable against  $\beta$ -lactamases with resistance to inactivation by renal dihydro peptidases. All Gram-negative bacteria and Gram-positive bacteria, with *P. aeruginosa*, are susceptible to doripenem in vitro, except MRSA and a few Enterococcus species. Studies comparing doripenem to meropenem or imipenem showed that doripenem had a more significant in vitro anti-pseudomonal effect.

### *P. aeruginosa* Treatment for Cystic Fibrosis Patients

The best locations to provide long-term care for CF patients are specialized care facilities, and *P. aeruginosa* therapy at these facilities often entails ongoing follow-up and sputum culture monitoring. This section intends to inform non-CF experts on the approach used at these institutions to treat persistent CF airway infections, including internists, pulmonologists, along with intensivists.

### Initial Colonization Treatment

Most CF patients will ultimately get a respiratory tract infection caused by *P. aeruginosa*, and it is thought that once this happens, it is almost tough to get rid of. A predominance of *P. aeruginosa* mucoid phenotypes characterizes the chronic disease. When *P. aeruginosa* is recognized on top of observation sputum or throat swab cultures, a strong antibiotic drug that primarily targets *P. aeruginosa* is attempted. These trials have shown that, when compared to untreated controls, this method reduces the likelihood of acquiring a long-term infectious illness, improves lung function, and cuts down on the number of hospital days. It is uncertain if this course of action will be effective in the long run for patients who relapse and need therapy.

### Chronic Stimulatory Therapy

When *P. aeruginosa* is repeatedly cultivated from CF patients' sputum for six months, the condition is commonly referred to as chronic *P. aeruginosa* infection. Once a persistent infection has been established, trials of planned intermittent antibiotic treatment have been conducted to see if this approach would affect the clinical course of the condition.

### Acute respiratory illnesses

Acute CF respiratory exacerbations have been treated with greater antibacterials as well as shorter intervals between doses than pneumonia in non-CF patients based on pharmacokinetic studies demonstrating enhanced drug authorization along with shortened removal half-life in CF patients. *P. aeruginosa* mucoid plugs stop the CF airway from absorbing the antibiotics. Antibiotic treatment frequently lasts from 14 to 21 days, depending on the seriousness of the symptom plus the prognosis.

For moderate pulmonary symptoms, oral ciprofloxacin at an amount of 29 mg/kg daily, split into a proposal or tid quantity delivery interval is often utilized. Intravenous antibiotics are used to treat more serious illnesses. Inhaled anti-pseudomonal medications are seldom utilized to treat acute pulmonary exacerbations despite being an essential part of CF patients' maintenance regimens owing to a lack of evidence.

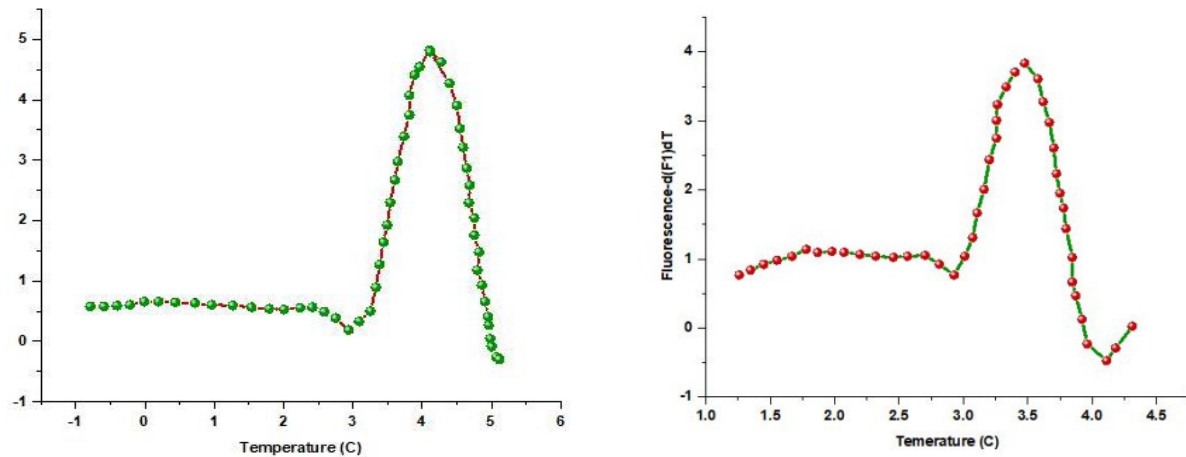
Table 3. Acute exacerbations of pulmonary CF are managed with anti-pseudomonal regimens	
Antibacterial	Dosage
One of the following:	
Cefepime	IV2gevery8hours
Ceftazidime	IV2gevery8hours
Meropenem	IV1gevery8hours
Plus:	
Tobramycin	IV3mg/kg every 8 hours <sup>b</sup>

The majority of CF clinicians advise administering two intravenous anti-pseudomonal drugs simultaneously to treat moderate to severe acute pulmonary exacerbations of CF despite the lack of compelling evidence.

Table 3 displays the typical treatment plans for adult CF patients at Washington University in Saint Louis. When selecting these first antibacterials, the most recent sputum culture results are often employed, and newly discovered sputum culture discoveries may alter them. Additionally, patients who have tested positive for various bacterial illnesses may get treatment designed mainly to ward against these strains.

*Real-time, fluorescence-based quantitative PCR*

The technique made it possible to find *P. aeruginosa* in CF patients more quickly. It created a real-time PCR technique that targeted the *gyrB* gene by utilizing melting curve analysis (MCA). This technique could easily differentiate *P. aeruginosa* from other microorganisms, as shown in Figure 3. Using 224 Gram-negative bacterial samples, a performance comparison of the real-time PCR approach and the Vitek detection system revealed that this method could successfully distinguish *P. aeruginosa* from other Gram-negative bacteria within 3 hours. A duplex real-time Polymerase Chain Reaction (PCR) test was developed against the genes *ecfX* and *gyrB* to address false-positive and false-negative concerns in identifying *Pseudomonas aeruginosa*.



**Figure 3.** Gram-negative bacilli MCA (a) Positive samples for *P. aeruginosa* had firm peaks with a consistent (b) Non-*P. aeruginosa* samples did not exhibit a peak at 87,9 °C

By contrasting the specificity and sensitivity of different genes, it was shown that real-time multiplex PCR could successfully resolve the conflict between sensitivity and specificity and identify *P. aeruginosa* from a mixed bacterial sample. An important pathogen in pneumonia and respiratory tract infections was also detected using real-time fluorescence-based PCR, which was a very sensitive, powerfully rapid, extensively applicable, and prospectively detectable method.

## CONCLUSION

*P. aeruginosa* is a dangerous bacterial pathogen known to cause CF patients' sino-pulmonary infections, nosocomial infections, and infections in immunocompromised hosts. Due to its many virulence features and antibacterial resistance mechanisms, *P. aeruginosa* has recently seen a surge in the prevalence of antibacterial resistance. Wherever possible, steps should be taken to avoid *P. aeruginosa* infections. Patients at high risk should also get the necessary first antimicrobial therapy. If the criminal detach with identified sensitivities be present and the disease is acute and uncomplicated, the de-escalation of antibacterials to a single medicine other than an aminoglycoside is supposed to be working in the context of a successful clinical response. People with CF are often treated for *P. aeruginosa* infections by CF specialists, while non-CF doctors may be able to help if their condition is severe. To treat MDR *P. aeruginosa*, doctors need to be knowledgeable about older antibiotics like Colistin, antibiotics that may be breathed for respiratory tract infections, and antibiotics that will probably be widely available shortly, such as doripenem.

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