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Review

Pseudomonas aeruginosa: Infections and novel approaches to treatment "Knowing the enemy" the threat of *Pseudomonas aeruginosa* and exploring novel approaches to treatment

Nikhil Sathe[a,b], Peter Beech[b], Larry Croft[b], Cenk Suphioglu[c], Arnab Kapat[a,*], Eugene Athan[d,*]

[a] *Reliance Life Sciences Pvt. Ltd., Dhirubhai Ambani Life Sciences Centre, Thane Belapur Road, Rabale, Navi Mumbai 400701, India*
[b] *School of Life and Environmental Sciences, Deakin University, Melbourne Burwood Campus, 221 Burwood Highway, Burwood Victoria 3125, Australia*
[c] *NeuroAllergy Research Laboratory, School of Life and Environmental Sciences, Deakin University, Geelong Campus at Waurn Ponds, 75 Pigdons Road, Waurn Ponds Victoria 3216, Australia*
[d] *School of Medicine, Deakin University, PO Box 281 Geelong 3220, Australia*

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ABSTRACT

Pseudomonas aeruginosa is an aerobic Gram-negative rod-shaped bacterium with a comparatively large genome and an impressive genetic capability allowing it to grow in a variety of environments and tolerate a wide range of physical conditions. This biological flexibility enables the *P. aeruginosa* to cause a broad range of infections in patients with serious underlying medical conditions, and to be a principal cause of health care associated infection worldwide. The clinical manifestations of *P. aeruginosa* include mostly health care associated infections and community-acquired infections. *P. aeruginosa* possesses an array of virulence factors that counteract host defence mechanisms. It can directly damage host tissue while utilizing high levels of intrinsic and acquired antimicrobial resistance mechanisms to counter most classes of antibiotics. *P. aeruginosa* co-regulates multiple resistance mechanisms by perpetually moving targets poses a significant therapeutic challenge. Thus, there is an urgent need for novel approaches in the development of anti-*Pseudomonas* agents. Here we review the principal infections caused by *P. aeruginosa* and we discuss novel therapeutic options to tackle antibiotic resistance and treatment of *P. aeruginosa* infections that may be further developed for clinical practice.

1. Introduction

Pseudomonas aeruginosa is a motile, nonfermenting, Gram-negative, rod-shaped [1] and blue-green pigmented bacterium belonging to the family *Pseudomonadaceae* [2,3]. The bacterium has a relatively large genome (5.5–7 Mbp) (Fig. 1) compared to other bacteria [4–6] and possesses a great genetic versatility [5,7] which enables it to grow in several different environments, to produce a variety of virulence factors and display antibiotic resistance to the majority of currently available antibiotics [8–13].

The bacterium is commonly isolated from natural resources like soil and surfaces in aqueous environments [14–17]. *P. aeruginosa* is also found on the skin of healthy people and has also been isolated from the throat (5%) and stools (3%) of nonhospitalized patients [17]. *P. aeruginosa* predominantly causes nosocomial infections such as pneumonia [18], infections of the urinary tract (UTIs) [19], wounds [20,21], bones and joints [22–24] and the bloodstream [25–27]. The bacterium also thrives when the epithelial barrier is damaged [28,29] neutrophil production is depleted [30], mucociliary clearance is altered [29] and in the presence of medical devices [31,32]. *P. aeruginosa* causes community-acquired infections such as gastrointestinal [33,34], skin and soft tissue infections [22,23] and otitis externa [25,35] and is known to be associated with lower respiratory tract infections in patients with cystic fibrosis [36]. Community-acquired pneumonia is rarely caused by *P. aeruginosa*; however, Wang et al. [37] reported one case of a healthy individual suffering from pneumonia, thought to be community-acquired, and caused by *P. aeruginosa,* which lead

* Corresponding authors.
E-mail addresses: Arnab.Kapat@ril.com (A. Kapat), e.athan@deakin.edu.au (E. Athan).

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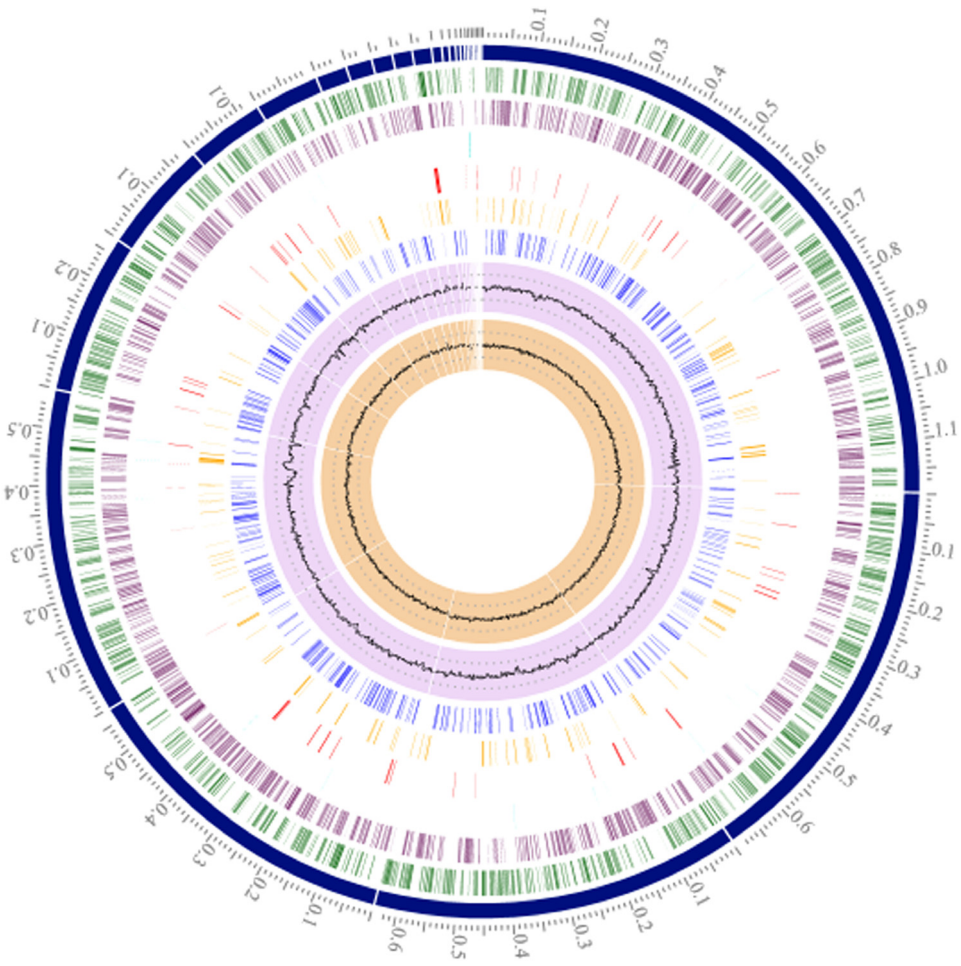

Fig. 1. Circular view of *P. aeruginosa* isolate EA31, showing from outer to inner rings: Position on contig in Mb, contigs ordered largest to smallest, forward CDS (green), reverse CDS (purple), noncoding genes (light blue), antimicrobial resistance genes (red), virulence factors (orange), transporters (dark blue), GC content, GC skew. Visualization, annotation and assembly by PATRIC 3.6.8.

to septic shock and multiple organ dysfunction syndrome.

Despite the discovery of several anti-*Pseudomonas* antibiotics [38,39], *P. aeruginosa* causes high morbidity and mortality [40,41] and remains difficult to treat because of its extensive and emerging antibiotic-resistance mechanisms [41,42]. *P. aeruginosa* is the second most common cause of ventilator-associated pneumonia in the United States [43], and ranks third among urinary tract infections associated with catheters [44]. It is the fourth leading cause of hospital-associated infections (HAIs) and accounts for 20% of all HAIs in Europe and United States [45] and is responsible for 75% of all deaths of severely burnt patients [46]. Furthermore, *P. aeruginosa* was found to be the fourth most common cause of mortality in patients with lower respiratory tract infection in India [47].

Alarmingly, the emergence of multidrug-resistant strains of *P. aeruginosa* is increasing and there are very few treatment options [48–50]. The World Health Organization (WHO) included carbapenem-resistant *P. aeruginosa* in the "Critical" category in a list of pathogens published in 2017 which require new antibiotics as a priority. On September 17, 2020, the Infectious Diseases Society of America (IDSA) published the first guidance document on infections caused by *P. aeruginosa* and categorized as difficult-to-treat resistance (DTR) [51].The resistance to antibiotics among *P. aeruginosa* strains is a result of the *de novo* [52,53] emergence of resistance after exposure to antibiotics, patient to patient transfer [13,54] of resistant bacteria and cross-resistance, which can result in multiple-drug-resistant (MDR) *P. aeruginosa* strains [52,55–57]. A scoping report on antimicrobial resistance in India reported a high prevalence of carbapenem resistance among *P. aeruginosa* (40%–47%); more than 50% of isolates were also reported resistant to broad spectrum antibiotics such as fluoroquinolones and third-generation cephalosporins [47]. Prakash et al. [9] reported 31.78% MDR *P. aeruginosa* in studies conducted in hospitals from India. Another study conducted to determine antibiotic resistance in *P. aeruginosa* isolated from tertiary care hospitals in India reported 47.7% were drug resistant, 50% MDR and 2.3% were extensively drug resistant (XDR) strains with a high level (80%) of carbapenems resistance [58]. Intra et al. [59] identified *P. aeruginosa* (6.17%) in COVID-19 patients. Xu et al. [60] isolated *P.*

aeruginosa from sputum samples. The isolates were found persistent in respiratory tract of the patient and were resistant to antibiotics.

High clonal diversity is often seen when studying the molecular epidemiology of *P. aeruginosa* isolates from hospital-acquired infections, CF patients, or the environment. The majority of isolates are connected to distinct genotypes, and a closer check reveals that this is only correct for isolates that are sensitive to antibiotics; isolates that exhibit MDR/XDR characteristics are not included. In fact, there have been numerous MDR/XDR strain epidemic breakout reports and alerts in the hospital setting for decades. The data from these studies and reports has added to the evidence of MDR/XDR global clones, often known as "high-risk" clones, spreading in numerous hospitals globally [61].

Colistin-only-sensitive (COS) profiles are frequent in many hospitals across the world, and pan-drug resistance has already been identified [61]. When *P. aeruginosa* is not susceptible to at least one antibiotic from at least three different antibiotic classes—penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems—it is said to as multi-drug resistant. The idea of "difficult-to-treat" resistance was put forth in 2018. DTR is described in this guidance as *P. aeruginosa* that does not display sensitivity to any of the following drugs: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.

Multidrug-resistant *P. aeruginosa*, also known as DTR-*P. aeruginosa*, typically arises from the interaction of several complex resistance mechanisms, such as reduced expression of outer membrane porins (OprD), hyperexpression of AmpC enzymes, increased activity of efflux pumps, and mutations in penicillin-binding protein targets [51]. *P. aeruginosa* has been found as a common co-infecting pathogen (23.8%) in COVID-19 patients leading to increase in the severity of the baseline illness [62]. Shafran et al. [63] also reported *P. aeruginosa* (25%) as a common coinfecting pathogen in COVID-19 patients. Russell et al. [64] identified *P. aeruginosa* frequently in sputum of COVID-19 patients. A special report on antibiotic resistance in the United States indicate that the rate of hospital-onset MDR *P. aeruginosa* cases increased by 32% in 2020 as a result of COVID-19 [65].

2. Infectious caused by *P. aeruginosa*

2.1. *Principal infectious caused by* P. aeruginosa

Hidron et al. [66] ranked *P. aeruginosa* on 6th position in the report published in 2006–2007 by the National Healthcare Safety Network (NHSN) at the Centers for Disease Control and Prevention (CDC) as the most common hospital-associated pathogen causing infections. Medical interventions such as mechanical ventilation [67,68], surgery [69], antibiotic therapy [70,71] and chemotherapy [72,73] are the major predisposing factors that may further cause serious *P. aeruginosa* infections in a hospital environment. The CDC published antimicrobial resistance threats in the USA in 2019 and categorized *P. aeruginosa* under "Serious threat level". The CDC also reported 32,600 hospitalized cases and 2,700 deaths leading to $767M attributable healthcare costs in

Table 1
Pseudomonas aeruginosa infections, causes and complications.

Infections	Causes	Complications
Bacterial keratitis	Ocular disease, postocular surgery, contamination of the lens or extended lens use [75]	Loss of vision, blindness [76]
Ear infection: otitis externa (Swimmers ear)	Contamination of water, prolonged exposure to moisture, insertion of foreign objects [75], ear plugs, ear phones [77].	Hearing loss [78]
Ear infection: chronic suppurative otitis media (CSOM)	Acute otitis media	Lateral sinus thrombosis, meningitis,cerebral abscess, otic hydrocephalus, extradural abscess, encephalitis [79]
Skin and soft tissue infections (SSTI)	Contaminated hot tubs or spa pools [80], whirlpools and swimming pools [81,82], leg waxing [81]	Ecthyma gangrenosum, subcutaneous nodules or progressive folliculitis with cellulitis [81]
SSTI – Gangrenous cellulitis and necrotizing fasciitis	Trauma or surgery, diabetes, vascular insufficiency [83]	Fulminant skin necrosis [82]
Green nail syndrome	Onycholysis, onychotillomania, microtrauma to the nail-fold, chronic paronychia, and associated nail disorders, such as psoriasis [84], diabetes mellitus, immunosuppression [85], frequent exposure to water or moist conditions [86]	Green-black discoloration of the nail bed [86]
Burn wound infection	Endogenous flora of the gastrointestinal and or upper respiratory tract [87,88]	Septicaemia [46]
Blood stream infections	Nosocomial [89]	Subcutaneous nodules, ecthyma gangrenosum and gangrenous cellulitis [82]
Urinary tract infections	Catheterization or surgery [75]	Sepsis in older patients, immunocompromised patients and individuals with diabetes [19]
Respiratory tract infections	Cystic fibrosis [90], mechanical ventilation [91], bronchiectasis [92]	Mortality [65,93]
Bone and joint infections	Osteomyelitis [94], haematogenous spread or exogenous and endogenous contiguous focus of infection [95]	Persistent infection [96]

the USA due to *P. aeruginosa* infections in 2017. Moreover, in a study conducted in a tertiary care hospital in North India in the years from 2012 to 2016, *P. aeruginosa* was identified as the pathogen in 95% of all infection cases [74]. Infections of *P. aeruginosa*, causes and complications are summarized in Table 1.

2.2. Burn wound infections

P. aeruginosa causes serious burn infections and sepsis was found as a major cause of deaths in patients [97]. Mortality as high as 75% was reported due to septicaemia caused by *Pseudomonas* spp. and other bacteria [98]. A study conducted in military hospitals in southern Jordan from June 1990 to May 1998 reported *P. aeruginosa* as a common cause (42.6%) of invasive burn wound infection [70]. Another study conducted in Al-Kendi hospital from October 2007 to June 2008 reported *P. aeruginosa* as a common cause (48.9%) of invasive burn wound infection [99]. The estimates by World Health Organization (WHO) reports 265,000 deaths annually due to burn injury, with nearly half of these occurring in the WHO South-East Asia Region [100,101]. Around 7 million people in India suffer from burn injuries every year, resulting in 140,000 deaths [102]. The major factors associated with burn wound infection are thermal destruction of the skin and concomitant depression of the local and systemic host cellular immune response [87,88]. Although burn wound surfaces are sterile immediately following thermal injury, within the first 48 hours microorganisms colonize the wound surface, which is rich in proteins and avascular necrotic tissue [87]. Wounds first become colonized by Gram-positive organisms such as *Staphylococcus aureus* and *Streptococcus pyogenes* before infection by *P. aeruginosa* [98,103,104]. Eventually, other bacteria and yeasts along with *P. aeruginosa* colonize wounds from patients' endogenous flora of the gastrointestinal and or upper respiratory tract [87,88]. Recent studies with the burn patients demonstrated that thermal injury results in impaired production of host defence peptides (β-defensins) in tissues surrounding the burn wound, and these peptides play a primary role in defence against *P. aeruginosa* [105–107]. The impairment of host immunity and loss of skin integrity allows opportunistic pathogens to enter the body and cause infection. For example, an experiment conducted in animals with partial cutaneous burns resulted in the development of fully grown *P. aeruginosa* biofilms in 48–72 hours [108]. The biofilm further reduces the effect of treatment of the wound as microorganisms in a biofilm are more resistant to antibiotic treatment [109]. Burn wound infection by *P. aeruginosa* manifests as a green pigment in subcutaneous fat, which is erythematous and later turns into a black, necrotic, nodular lesion [70]. A retrospective study conducted between April 2007 and January 2010 in the burn unit at Red Cross War Memorial Children's Hospital in Cape Town, South Africa, *P. aeruginosa* was isolated from 14.5% patients. These isolates were resistant to povidone-iodine (92.5%), piperacillin-tazobactam (36.1%) and tobramycin (3.3%) [110]. A study conducted in India found *P. aeruginosa* in 54.9% of burn patients with high-level (76.8%) of multidrug resistance [111].

Gonzalez et al. [21] conducted a study to monitor the effect of burn wound exudate on growth and expression of virulence factors of *P. aeruginosa*. The results of this study indicated that *P. aeruginosa* can grow in burn wound exudate with a lowered doubling rate compared to its normal control, whereas other common burn wound pathogens failed to grow. An increase in expression of all virulence factors such as quorum sensing, pyocyanin, pyoverdine, elastase, rhamnolipid was also observed when *P. aeruginosa* was grown in burn wound exudate. This study explained a reason for *P. aeruginosa* being a predominant pathogen in burn victims.

An intracellular signaling molecules such as 4-hydroxy-2alkylquinolines (HAQs) are involved in iron chelation governs and dictate the infection course, Que et al. [112] for the first time showed that clinically important specimens of *P. aeruginosa* isolated from active burn wound infection from human patients produce and excrete detectable levels of HAQs.

2.3. Bacterial keratitis

P. aeruginosa causes keratitis in patients with ocular disease, postocular surgery and in individuals who use contact lenses. Most of the contact lens-associated *P. aeruginosa* infections are due to contamination of the lens or extended lens use—resulting in disruption of the epithelial surface of the cornea that further leads to corneal abrasions [75]. When epithelial barrier function is impaired by using contact lenses for long periods, *P. aeruginosa* causes an opportunistic infection. *P. aeruginosa* becomes rapidly internalized by binding to toll-like receptors (TLR5) on the surface of the cornea [113]. Keratitis due to *Pseudomonas* is characterized by sudden onset, rapid progression of ocular pain, redness, tearing, photophobia, and blurred vision. Clinically, this infection causes corneal epithelial defect and a stromal infiltration that further leads to stromal necrosis and progressive thinning [114]. *P. aeruginosa* causes potentially blinding condition as a complication of keratitis [115]. *P. aeruginosa* is responsible for causing bacterial keratitis in 6% to 39% of the cases in the USA [116,117] and 8% to 21% in south India [116]. *P. aeruginosa* infections are also reported after exposure to ultraviolet rays (260–280 nm) and frequently occur in people who are exposed to sun lamps and individuals who don't use proper shields during welding [118]. Bacterial keratitis may cause loss of vision and, in severe cases, even blindness [76].

2.4. Ear infections

Inflammation or infection of the external auditory canal, referred to as otitis externa or "swimmers ear", is caused by *P. aeruginosa.* Otitis externa is associated with contamination of water by *P. aeruginosa*, prolonged exposure to moisture, and insertion of foreign objects [75]. *P. aeruginosa* is one of the major organism to cause chronic suppurative otitis media (CSOM), also referred to as chronic active mucosal otitis media, chronic otomastoiditis and chronic tympanomastoiditis. The bacterium causes chronic inflammation of the middle ear and mastoid cavity that further results in recurrent ear discharge [119] or otorrhoea hearing loss through perforation of the tympanic membrane [119,120]. CSOM may cause common ear discharge, hearing loss [121] or, rarely, complications such as fever, otalgia, vertigo, meningitis, facial nerve palsy, and brain abscess. Mittal et al. [122] using human and animal cell based assays demonstrated that otopathogenic *P. aeruginosa* are able to enter and survive inside macrophages. Molecular mechanism elucidated uptake of bacteria by human and animal cells is dependent on actin polymerization whereas OprF expression plays important role in intracellular survival of *P. aeruginosa.* Tertiary care centre in Uttarakhand, India, conducted a study to know the prevalence of *P. aeruginosa* among patients suffering from CSOM. The results of this study indicated *P. aeruginosa* as a major cause of CSOM (32.1%) with substantial number of MDR strains [119]. More than 700 million cases of CSOM are reported globally per annum, with children below age 5 found to be more vulnerable to *P. aeruginosa* [120].

2.5. Skin and soft tissue infections (SSTI)

Folliculitis starts with sudden onset of numerous, large, monomorphic, painful papules, and pustules that develop approximately 24 hours after prolonged immersion in contaminated hot tubs or spa pools [80], whirlpools and swimming pools [81,82] or after leg waxing [81]. The lesions often congregate on body parts in contact with contaminated water [82] and usually appear 8–48 hours after exposure [81]. In immunosuppressed patients, folliculitis can further progress to ecthyma gangrenosum. In AIDS patients, *P. aeruginosa* infection may cause subcutaneous nodules or progressive folliculitis with cellulitis [81]. Another complication found in children is a "hot-foot" syndrome. It is characterized by painful plantar nodules [82].

2.6. SSTI – Gangrenous cellulitis and necrotizing fasciitis

P. aeruginosa infection of the skin and fascial layers is a rare but serious medical condition. It is characterized by rapid and progressive destruction and inflammation that further results in fulminant skin necrosis and death. The spread of necrotizing fasciitis is directly proportional to the thickness of the subcutaneous layer as it moves along the fascial plane. Another complicated infection that *P. aeruginosa* causes in immunocompromised elderly individuals is necrotising fasciitis: a rare but serious infection of subcutaneous tissue and fascia. A specific variation of necrotising fasciitis is referred to as Fournier's gangrene; *P. aeruginosa* infection in these patients results in scrotal discomfort and malaise that further lead to perineal pain, swelling, blisters, and necrosis [82].

2.7. Green nail syndrome/chromonychia/Fox-Goldman syndrome

Persistence of pyocyanin in the nail plate and involvement of *P. aeruginosa* was first described in 1944 by Goldman and Fox and hence named after them [123]. Patients with underlying conditions such as onycholysis, onychotillomania, microtrauma to the nail-fold, chronic paronychia, and associated nail disorders, such as psoriasis [84], diabetes mellitus, immunosuppression [85] and people who are frequently exposed to water or moist conditions suffer from green nail syndrome, as the causative agent, *P. aeruginosa,* thrives in moist conditions. The condition is characterized by onycholysis and green-black discoloration of the nail bed, it is most often associated with chronic paronychia [86]. Chernosky and Dukes (1963) demonstrated the presence of *P. aeruginosa* within the nail plate and the green discoloration of the nails is due to pyocyanin produced by *P. aeruginosa* [82]. Green nail syndrome is commonly restricted to one or two nails with partial or complete involvement of the nail plate [123,85]. The infection is characterized by painless nail plate with erythematous or tender skin around the nail. An infected individual can autologously disseminate the bacterium by scratching or rubbing his or her skin, especially when cutaneous surface is damaged [123]. A retrospective study conducted to investigate fungal coinfection with *P. aeruginosa* during the period of 2015–2018 reported green nail syndrome commonly affected great toe nail (69.9%) and high prevalence of fungi [124].

2.8. Bacteraemia

Blood stream infections (BSI) caused by *P. aeruginosa* are often fatal. The bacterium is responsible for 3%–7% of blood stream infection cases with high morbidity and mortality rates (27%–48%) in critically ill patients [125,126]. Wisplinghoff et al. [89] published a nationwide surveillance study on nosocomial BSI in the USA and reported *P. aeruginosa* as the third most common Gram-negative bacteria causing nosocomial BSI and accounted for 4.3% of all cases. In the ICUs, *P. aeruginosa* accounted

for 4.7% of all cases and was reported as the fifth most common isolate implicated in BSI, and the seventh most common isolate in non-ICU wards, accounting for 3.8% of cases. The great majority of reported crude mortality percentages from large surveillance studies range from 39% to 48%. Systemic *P. aeruginosa* infections cause subcutaneous nodules, ecthyma gangrenosum and gangrenous cellulitis. Patients with burns and AIDs are more vulnerable to systemic infection by *P. aeruginosa* [82].

BSI due to *P. aeruginosa* is an important cause of morbidity and mortality in neutropenic cancer patients. Gudiol et al. [95] retrospectively studied *P. aeruginosa* BSI cases from January 2006 to May 2018. *P. aeruginosa* strains isolated from adult neutropenic oncohematological patients, including hematopoietic stem cell transplant recipients, were caused by multi drug resistant (25.4%) and extensively drug resistant bacteria (19.3%). The highest rate of multi drug resistance was observed in Colombia and Argentina. Hickey et al. [126] using *Galleria mellonella* model demonstrated that the virulence factors such as LecA, RpoN, and proteins involved in cellular metabolism and replication isolated from BSI *P. aeruginosa* are increased relative to its peripheral counterparts.

2.9. Urinary tract infections (UTIs)

P. aeruginosa is an important uropathogen [19], associated with 7%–12% of all nosocomial urinary tract infections [44,127]. The bacterium usually causes UTIs following catheterization or surgery [75]. UTI is the second most common type of infection in the body [127]. *P. aeruginosa* was found to be the third most common Gram-negative pathogen causing 7.1% of all nosocomial urinary tract infections in surveillance studies from the Asia-Pacific region in 2009 to 2010 [128]. Bitsori et al. [129] studied *P. aeruginosa* UTI cases in children with *E.coli* UTI cases. Results indicated more complications and antibiotic resistance pattern. A retrospective study conducted during September 2012–September 2014 to study mortality rates in hospitalized patients with *P. aeruginosa* UTIs, reported 17.7% mortalities at 30 days and 33.9% mortalities at 90 days [130]. Shobha et al. [131] collected 107 urine samples from microbiology laboratory during 2015–2016 reported 84.11% *P. aeruginosa* UTIs. Results of this study indicated majority of UTIs with *Pseudomonas* species were found in males and observed more in age group more than 60. Studies on nosocomial urinary tract infections occurring in the intensive care unit (ICU) report even higher rates of *P. aeruginosa*. Studies by national French nosocomial surveillance reported 16% of UTIs were caused by *P. aeruginosa* and strains isolated in the study also showed higher rates of antimicrobial resistance [132]. A study conducted to demonstrate virulence and antibiotic resistance patterns in *P. aeruginosa* isolates from UTIs among children in southern Poland reported *exoY* as most prevalent virulence gene and sensitivity of isolates to beta-lactams, aminoglycosides and colistin; however, large proportion of isolates were resistant to carbapenems and fluoroquinolones [133]. Badamchi et al. [134] conducted a study to detect virulence genes and antimicrobial susceptible pattern in children with UTI in Tehran, reported *lasB* as most prevalent virulence gene and cefotaxime as a least effective antibiotic. *P. aeruginosa* is also known to invade epithelial and mast cells [135]. *P. aeruginosa* urinary infection may cause complications such as sepsis that can be fatal in older patients, immunocompromised patients and individuals with diabetes [19]. Disruption of the epithelial layer during application of a catheter promotes bacterial colonization [75] and the formation of biofilm [127]. Catheter-associated UTI accounts for 20% to 49% of all nosocomial infections; the pathogen enters via extraluminal or by intraluminal route of the catheter [127]. Penaranda et al. [135] demonstrated that *P. aeruginosa* can survive intracellularly in bladder epithelial cells, sets a stable infection and become tolerant to antibiotics *in vivo* and *in vitro* model. Estaji et al. [136] isolated 70 *P. aeruginosa* strain from patients with UTI hospitalized in different wards in Iran. Findings of this study showed high genetic diversity among the strains isolated from different patients; 35% of these cases were catheter associated UTIs. Isolated strains were also demonstrated resistance to beta-lactam antibiotics and identified with SHV and TEM genes. *P. aeruginosa* causes 1%–4% UTIs after flexible cystoscopy [137,138]. Sorbets et al. [138] reported an outbreak of UTIs which reached to 10.18% after urinary bladder exploration with contaminated cystoscope.

3. Respiratory tract infections

3.1. Cystic fibrosis

Cystic fibrosis is a common autosomal recessive genetic disease among Caucasians with one in 2,500–4,000 people affected [90,139–142]. The disease is characterized by a mutation in the gene for cystic fibrosis transmembrane conductance regulator (CFTR) protein [90,143]. Dysfunction of the CFTR channel causes hyper sodium absorption [90] and impaired mucociliary clearance [90,140]. In addition to obstructing airways, mucous creates a hypoxic environment that favors the colonization of *P. aeruginosa*. Other factors that contribute to *P. aeruginosa* infection are impaired function of antimicrobial peptides, increased availability of bacterial receptors, defective internalization of bacteria by epithelial cells and low levels of defensive agents such as nitric oxide and glutathione [90]. The lung environment in cystic fibrosis patients is different from that of a healthy individual's [141], and factors which affect bacterial colonization are osmotic stress due

to the viscous mucus, oxidative and nitrosative stresses due to host responses, sub inhibitory concentrations of antibiotics and the presence of other microorganisms [143]. To overcome these challenges, *P. aeruginosa* undergoes an evolutionary change to adapt to the cystic fibrosis environment: it adapts to the cystic fibrosis lungs by overproducing the polysaccharide, alginate, and undergoing auxotrophic mutations, loss of motility and elevated mutation rate due to a faulty DNA repair mechanism [143]. Once *P. aeruginosa* colonizes the lung of a patient with cystic fibrosis, it becomes difficult to eradicate and can be fatal [141,144,145]. During infection, macrophages assemble inflammasome, a cell to cell signaling platform that promotes inflammation. *P. aeruginosa* from cystic fibrosis patients are unable to induce activation of inflammasomes. This unique mechanism was observed among all the patients and times of infection [146]. LaFayette et al. [147] demonstrated a mechanism by which cystic fibrosis adapted *P. aeruginosa* lasR mutants induce neutrophil dominant hyper inflammatory response and thereby amplify the inflammation and accelerate disease progression.

3.2. Pneumonia

Pneumonia is caused by *P. aeruginosa* and is divided into four categories: (1) Hospital-acquired pneumonia, which occurs 48 hours or more after hospitalization; (2) Ventilator-associated pneumonia that develops more than 48 to 72 hours after endotracheal intubation; (3) Health care-associated pneumonia occurs among nonhospitalized patients, who live in a nursing home or long-term care facility, those received intravenous antimicrobial therapy or chemotherapy or wound care, and those who attended a hospital or dialysis clinic in the previous 30 days of the current infection [148–150] and (4) Community acquired pneumonia. *P. aeruginosa* is a rare cause of community-acquired pneumonia, but it does occur more frequently in some areas than others. *P. aeruginosa* is nearly always isolated from elderly patients with concomitant diseases, most notably COPD, rather than from community-dwelling patients. An increase in *P. aeruginosa* infections in nursing home residents serves as a good illustration of this. There are case reports of CAP in healthy people, but all of them were also smokers [151].

As per the 2004–2006 National REA-RAISIN surveillance data, which reported *P. aeruginosa* to be the most common cause of pneumonia (25%) among all Gram-negative and -positive pathogens [133]. Weber et al. [91], estimated that more than 90% of the ventilator-associated pneumonia occurred in patients housed in ICUs, whereas 67% of hospital-associated pneumonia occurred in patients not housed in ICUs. *P. aeruginosa* accounted for 17.5% of all cases in ventilator-associated pneumonia and 9.26% of all cases in hospital-associated pneumonia [91]. Reported percentages of *P. aeruginosa* implicated in community-acquired pneumonia vary from 0.3% to 11%, whereas it varies from 2.2% to 20% in healthcare associated pneumonia [150,151].

Morello et al. [152] demonstrated the role of LoxA expression using clinical isolates of *P. aeruginosa*. It was observed that several clinical isolates of *P. aeruginosa* express LoxA. Gene product when secreted in lungs, it processes a wide range of host polyunsaturated fatty acids that results in production of bioactive lipid mediators. It also inhibits secretion of major chemokines and recruitment of leukocytes. Overall, LoxA expression promotes persistence of bacteria in lung environment and plays important role in pathogenesis. Mutation in mucA gene results in overproduction of alginate polymer, which results in the mucoid phenotype and provides protection to *P. aeruginosa*. In a retrospective study conducted during 2012–2014, 75 patients with *P. aeruginosa* pneumonia treated at a tertiary referral hospital in South Korea were studied. The data from this study illustrated that mutation in mucA gene can be considered as an independent predictor of mortality [153].

3.3. Bronchiectasis

Chronic bronchial dilatation is referred to as bronchiectasis. As a result, there is inadequate mucus drainage and increased risk of bacterial infection. Patients with cystic fibrosis, other forms of bronchiectasis, and severe chronic obstructive pulmonary disease are particularly vulnerable to *P. aeruginosa* since it is an opportunistic bacterium. Despite extensive intravenous antibiotic therapy, *P. aeruginosa* is seldom eliminated once it develops into a chronic infection in bronchiectasis. Chronic infection is linked to more severe airflow restriction and more extensive lung damage [92]. Davies et al. [92] evaluated the rate of pulmonary function decline in individuals with and without *P. aeruginosa* infection. The findings imply that *P. aeruginosa* is a marker of disease severity but does not hasten a decline in pulmonary function. *P. aeruginosa* is one of the most prevalent bacteria that colonize bronchiectasis in people without cystic fibrosis. *P.* aeruginosa was estimated to have a persistent colonisation in about 25% of people with non-CF bronchiectasis [154]. In a cross-sectional cohort study with non-CF bronchiectasis in the year 2018, Kwok et al. [154] found that *P. aeruginosa* was a commonly isolated organism that accounted for about 27% of the entire cohort. In comparison to non-*P. aeruginosa* colonized patients, these patients had larger sputum volumes, higher FEV_1 and FVC, more than three lobes were impacted in 66% of cases, 24% of patients needed hospitalisation, and 18% required long-term macrolide therapy.

3.4. Bone and joint infections

Usually bones and joints are sterile areas, but bacteria can reach such sites by haematogenous spread or exogenous and endogenous contiguous focus of infection [155]. In a study of 454 patients with osteomyelitis, *P. aeruginosa* was implicated in 4.4% of all cases [94]. Tummala et al. [155] reported *P. aeruginosa* as the most common pathogen causing osteomyelitis among Gram-negative organisms. Recurrence rate of osteomyelitis caused by *P. aeruginosa* was reported more than two-fold compared to infection caused by *Staphylococcus aureus* [94]. *P. aeruginosa* has been implicated in 10% of all cases of sternoclavicular septic arthritis, for which common risk factors include intravenous drug use, diabetes mellitus, trauma and infected central venous lines [156]. Cerioli et al. [96] retrospectively studied 1,638 implant associated bone joint infection patients over 7 year (2011–2017) period. Ninety patients (5.5%) among them were found infected with *P. aeruginosa*. During prolonged follow-up, 23 patients experienced treatment failure whereas 7 patients experienced persistent infection and required prolonged antibiotic treatment as long as 3 months. Septic arthritis of wrist joint due to *P. aeruginosa* is a rare condition in children and characterized by acute onset of fever, swelling and pain [157].

4. Novel approaches to treat *Pseudomonas* infections

The antimicrobial resistance in *P. aeruginosa* is increasing steadily; as a result, the treatment of infections caused by *P. aeruginosa* is extremely challenging. Despite recent advances in the field of anti-bacterials, the number of new antibiotics under clinical development remain limited and their introduction into the market is extremely slow. Thus, there is an urgent medical need for innovative options to be developed for the treatment and management of infections caused by *P. aeruginosa*. Novel therapeutic options for treating *P. aeruginosa* infections are summarized in Table 2.

4.1. Quorum sensing inhibition

Bacterial communication can be inhibited using quorum-sensing inhibitors. Production of most of the virulence factors is regulated by quorum sensing and it is a prime therapeutic target [158]. This approach relies on the reduction of virulence rather than killing the pathogen; it may result in a reduction in the evolution of antibiotic resistance and enhance the treatment of multidrug-resistant pathogens [172]. The *P. aeruginosa* quorum-sensing system is comprised of *las* and *rhl*, the gene products of which help bacteria produce virulence factors and form biofilms [160,173–176]. Quorum sensing can be inhibited by different mechanisms such as signal generation, signal molecule degradation, preventing accumulation of signal molecules and antagonism of the signals' mode of action [158].

Potential candidates having quorum-inhibiting or -quenching activity have been found in chamomile, carrot [158,177], garlic [158,159,177], salicylic acid [158,160,178] and algal furanone [158,161,179]. The effect of garlic formulation on quorum-sensing inhibition was studied in a small pilot, randomized, controlled clinical trial in adults and children with cystic fibrosis and chronic *P. aeruginosa* infection. The garlic formulation did not cause significant improvement in clinical parameters and there was no reduction in the levels of quorum sensing molecules in plasma and sputum samples [180]. Brominated furanones studied in a reporter-gene assay have been found to be inhibitory against *P. aeruginosa* quorum-sensing system (*las* and *rhl*), resulting in inhibition of production of virulence factor elastase B and biofilm depletion [181]. Plant essential oils, such as clove oil, were found to inhibit swarming motility and quorum sensing [182–184]. Other synthetic chemicals, such as metabromo-thiolactone and metachlorothiolactone, inhibited quorum sensing-regulated virulence factor pyocyanin [176]. Alginate oligomer (OligoG CF-5/20) was found to inhibit global regulatory QS signaling and swarming motility in *P. aeruginosa* [185]. DNAse I treatment in *P. aeruginosa* biofilms produced *in vitro* conditions also have been found to reduce biofilm matrix [186].

Table 2
Novel therapies for treating *Pseudomonas aeruginosa* infections.

Novel therapeutic agents	Mode of action/target	Reference
Quorum sensing inhibitors	Signal molecule degradation, preventing accumulation of signal molecules and antagonism of the signals	Chamomile, carrot [158], garlic [159], salicylic acid [160], furanones [161]
Immunotherapy	PcrV protein, flagellin, LPS	KB001-A [162], Immunoglobulin Y [163], Panobacumab [164]
Iron chelators	Chelation of the environmental iron	Gallium [165]
Vaccines	Polysaccharide, PcrV,OprI,Hcp1, FlgE, fructose bisphosphate aldolase, OprH gene product	PcrV-OprI-Hcp1-Trivalent vaccine [166], Polyvalent vaccine [167]
Herbal medicine	Exopolysaccharide production, phenazine pyocyanin, rhamnolipids, elastase and alkaline protease	Tanreqing [168], *Herba patriniae* [169]
Phage therapy	Lysis of cell membrane and wall	Pf3R [170], Genetically engineered synthetic phages [171]

4.2. Immunotherapy

KB001-A is recombinant anti-*Pseudomonas* PEGylated monoclonal antibody. KB001-A antibodies inhibit the action of type III secretion system T3SS in *P. aeruginosa*. KB001-A specifically targets the PcrV protein component of the T3SS tip and blocks its activity [162,187,188]. In 16-week safety and efficacy trial, KB001-A was well-tolerated and found to be safe with no significant unfavorable effects. Overall, treatment caused reduction in sputum inflammatory factor (IL-8) [162].

Anti-*Pseudomonas* immunoglobulin Y antibodies are produced from chicken egg by immunizing them with *P. aeruginosa*. These antibodies specifically bind to *P. aeruginosa* flagellin and decrease their ability to attach to epithelial cells and cause lung infection. A Phase I study was conducted in patients with CF: patients were asked to gargle with IgY antibodies, and the study concluded that none of the patients became chronically colonized and no undesirable side effects were reported [163]. A recent Phase III clinical trial to investigate the anti-*Pseudomonas* activity of IgY is underway [186]. Another human monoclonal antibody (IgM) targeting the bacterial LPS [189–191], panobacumab, was reported safe with low recurrence of pneumonia in a phase IIa clinical trial in nosocomial pneumonia [164].

4.3. Iron chelators

P. aeruginosa needs iron for its growth, the formation of biofilm and its survival [192]. It sequesters iron from the environment by secreting the siderophores pyoverdin and pyochelin [193]. The human innate immune system recognizes and blocks biofilm development by secreting lactoferrin. Lactoferrin chelates the iron, causing *P. aeruginosa* to increase twitching motility rather than forming aggregates and biofilm [194]. Gallium has been found to have antimicrobial activity [165,192,193,195]. Biological systems mistakenly take up gallium as it has an ionic radius similar to Fe^{3+}, but gallium lacks the redox activity of iron and hence it inhibits iron-dependent processes [193,195]. Gallium was also found effective in a mouse lung infection model, with approximately 1,000-fold decrease in the number of bacteria in the lungs [195]. Only one phase I pharmacokinetic study using gallium nitrate with two different doses (100 and 200 mg/m^2/day) was conducted in patients with CF, with no adverse effects observed and the study showed promising results for the clinical application of gallium nitrate [195]. A combination of gallium with an antibiotic preparation has been found to enhance the activity of antibiotic: for example, gallium-gentamycin liposomal coencapsulation was found to be more effective than gentamycin alone in eradicating MDR *P. aeruginosa* growing in planktonic or biofilm community [196,197]. Similarly, the combination of deferasirox and tobramycin was found to significantly prevent the formation of biofilm on CF epithelial cells [197].

4.4. Vaccines

There are no licensed vaccines against *P. aeruginosa* at present [166,198]. An octavalent, polysaccharide, toxin-conjugate vaccine developed by the Swiss Serum and Vaccine Institute was studied in the European CF community. The study concluded the persistence of antibodies in vaccinated patients with a significantly lower rate of infection. Later, a double-blind, placebo-controlled study conducted to evaluate the safety and efficacy of flagella vaccine in patients with CF, showed a lower risk of *P. aeruginosa* infection [199]. Another approach used OprF-OprI outer membrane fusion protein as an antigen [198]: human volunteers were vaccinated with systemic, nasal or oral live vaccine followed by a systemic booster and resulted in enhancement of specific IgA antibodies at the pulmonary airway surface; immunization resulted in a rise in serum antibody titers. The study concluded nasal and oral vaccines could be promising candidates for the development of anti-*P. aeruginosa* immunization [200]. Further phase II studies resulted in significant immunogenic responses against *P. aeruginosa* [201]. The efficacy of the trivalent vaccine (PcrV-OprI-Hcp1) was studied in mice models and resulted in a significant reduction in acute skin infection and pneumonia due to *P. aeruginosa* [166]. Wan et al., [202] studied the effect of recombinant vaccine in *P. aeruginosa* infected mice. This promising vaccine candidate is a flagellar antigen FlgE (reFlgE) isolated from sera of patients recovered from *P. aeruginosa* infection found to induce a Th2 cell-mediated response. Anti-reFlgE antibodies produced in mice were found to reduce bacterial load and inflammation in mice.

Another innovative new vaccine candidate used Pf phage, a filamentous bacteriophage isolated from chronic diabetic wound has been shown to increase virulence of *P. aeruginosa*. The vaccine formulation containing peptide from Pf phage coat protein conjugated to the carrier protein CRM197 combined with novel adjuvants and delivery systems shown to induce humoral immunity as well as cell-mediated response against Pf phage peptide. The overall effect provided protection from establishment of *P. aeruginosa* in mice [203].

An immunoinformatics tool based study predicted an effectiveness of epitope based vaccine against an enzyme fructose bisphosphate aldolase (FBA) produced by *P. aeruginosa.* This prediction study analyzed possible epitopes for B and T cells. Results indicated 6 MHC-I and four MHC-II promising epitopes. Further *in vitro* and *in vivo* studies are required to prove the efficacy of epitope based vaccine [204].

Another novel approach by Cabral et al. [205] studied immunogenicity and protective efficacy of a live vaccine against *P. aeruginosa.* A vaccine consists of an auxotrophic strain which lacks the key enzyme involved D-glutamate biosynthesis, a key component of bacterial cell wall. The trace amount of glutamate present in *in vivo* condition doesn't allow bacteria to synthesize cell wall and thereby compromise the growth of the cells without affecting the immunogenic properties of the bacteria. When administered intranasally in mice, a vaccine induced systemic and mucosal antibody production, also stimulated effector memory, central memory, IL-17A-producing CD4+ T cells, and recruited neutrophils and mononuclear phagocytes into the airway mucosa. Intranasal administration also significantly improved survival rate in mice infection model.

Reverse vaccinology approach integrated with bioinformatics tool was used for selection of 52 potential *P. aeruginosa* antigens. These antigens were conserved in *P. aeruginosa* genomes from different origin. The combination of selected antigens effectively controlled *P. aeruginosa* infection in murine pneumonia and acute respiratory infection model [206].

Liu et al. [207] found OprH gene product as a potential vaccine candidate for prevention of lung infection caused by *P. aeruginosa*.

A novel polyvalent irradiated *P. aeruginosa* vaccine developed by Ahmed et al. [208] contains inhibited pathogen with functional antigenic expression. Administration of vaccine by intranasal, intramuscular and subcutaneous route followed by challenge test resulted in 95% protective efficacy in murine model.

4.5. Lectin inhibitors

These proteins recognize sugar residues on the cellular surface and permit bacterial cells to cross-link and form aggregates leading to further formation of biofilms [158,209,210]. LecA and LecB have fucose-specific [158,211,212] and galactose-specific binding sites and hence can be blocked by competitive inhibitors [158,212,213]. A randomized trial with a small group of CF patients who received fucose/galactose inhalation treatment resulted in significant reduction of *P. aeruginosa* colony forming units from sputum and tumor necrosis factor α levels [158].

Production of hypothiocynate is another innate immune defence but, in patients suffering from CF, epithelial cells do not produce thiocyanate [193]. Hypothiocynate is a bactericidal agent produced by oxidative lactoperoxidase-hydrogen peroxide thiocyanate system. This system was found to be defective in patients with CF. The combination of lactoferrin and hypothiocyanate [158,214] was found to be bactericidal and prevent biofilm formation by *P. aeruginosa* on airway epithelial cells. The combination named ALX-009 (Meveol) was granted orphan drug status in 2009. Studies with combination resulted in a significant decrease in total sputum bacterial density following a single dose. However the number of bacteria was found to increase after treatment was discontinued [215].

4.6. Alternative herbal medicine

Fu et al. [169] constructed a luxCDABE-based reporter system to monitor the expression of 6 key biofilm-associated genes in *P. aeruginosa.* A library of 36 Chinese herb extracts were screened for their inhibitory properties against the genes involved in biofilm formation and found that the extracts of *Herba patriniae* displaying significant inhibitory effect on almost all biofilm associated genes and it altered the structure of the mature biofilms. Further experiments also indicated decreased exopolysaccharide production by biofilm forming *P. aeruginosa* and promoted its swarming motility.

A study conducted to determine antimicrobial activity of five endemic plants (*M. macrocarpa, D. loretense, T. impetiginosa, E. camaldulensis* and *U. tomentosa*) commonly used in traditional medicine in the Amazon and sierra regions of Peru exhibited significant *in vitro* efficacy against *P. aeruginosa* [216].

A traditional Chinese medicine Tanreqing (TRQ) formula was found to completely inhibit the production of phenazine pyocyanin and moderately inhibit the production of virulence factors such as rhamnolipids, elastase and alkaline protease. A transcriptomic studies indicated that the treatment attenuates the expression of QS-regulated genes in *P. aeruginosa* [168].

4.7. Phage therapy

A promising approach to treat *P. aeruginosa* infection is using abundant and self-replicating viruses known as bacteriophages. Bacteriophages are viruses that infect bacteria. Also known simply as phages, bacteriophages are ubiquitous, obligate parasites, which require a bacterial host to replicate. Bacteriophages attach to the host bacterium and hijack the cell's replicative machinery, thus disrupting bacterial metabolism and causing the bacterial host to lyse [217–219]. Bacteriophages are very species-specific and they form a part of the normal flora of the human body. Bacteriophage therapy does not induce hypersensitivity reactions in patients and acts on targeted bacterial species without affecting the normal bacterial flora. Unlike antibiotics, it is very easy to search for new phages against bacteriophage-resistant bacteria, whereas developing a new antibiotic requires several years. Commercial manufacturing of antibiotics is a complex and costly process, whereas bacteriophages can be produced easily in a cost-effective manner. Bacteriophage treatment can be performed with a very small dose, as phages

multiply and increase their number at the site of the infection [220–222]. Currently, phage therapy is practised in eastern European countries with centres in Warsaw, Poland, and Tbilisi, Georgia. Anti-*Pseudomonas* cocktails are sold in pharmacies in Georgia and Russia. A few case studies conducted in Belgium and the U.S. reported successful treatment of infections with MDR *P. aeruginosa*. Very few reports of bacteriophage treatment for *P. aeruginosa* infection are available in the years from 1990 to 2018. Phages alone, or in combination with antibiotics, were employed to treat infections such as chronic otitis [223], burn wound infection [224,225], UTI [226], sepsis [227], pneumonia, endocarditis, lung infection, bacteraemia [228], and graft infection [229], and resulted in an improvement in conditions of the patients with a concomitant reduction in the number of *P. aeruginosa* and no recurrent infection [230].

Another approach used nonreplicating phages for delivery of genes encoding proteins toxic to the bacterial pathogen. A genetically engineered filamentous phage (Pf3) of *P. aeruginosa* was modified by inserting restriction endonuclease gene in place of export protein gene. The variant nonreplicating, nonlytic phage Pf3R was studied in mice infection model and found to reduce endotoxin from target cell thereby increased the survival rate [170].

Pires et al. [171] designed and assembled first genetically engineered synthetic phage. The genome size of phage was reduced by knocking out up to 48% genes encoding hypothetical proteins. The resulting *P. aeruginosa* phage (vB_PaeP_PE3) was found as efficacious as its wild type. This experiment revealed a novel strategy to clear space from phage genomes in order to introduce genes of interest and potentiate the future treatment of *P. aeruginosa* infections.

Aghaee et al. [231] proposed combination of phages and antibiotics may increase treatment efficacy and prevent resistance development. An *in vitro* study involving single phage, mixture of two phages and combination of antibiotic and phages were tested against *P. aeruginosa* isolated from burn patient. A combination of 2 phages with antibiotic resulted in better efficacy than other formulations.

5. Novel approaches to inhibit *Pseudomonas* biofilms

A biofilm is a complex matrix of extracellular polymeric substances that includes glycopeptides, lipids and lipopolysaccharides which protect bacteria from extreme conditions. The matrix allows inflow of nutrients, water and signalling molecules [232,233]. Bacteria in a biofilm are found to be 1,000-times less susceptible to antimicrobial therapy than those that are not [109] hence new management strategies are needed for infections caused by *P. aeruginosa* that result in biofilm development. The exopolysaccharides, Psl, Pel and alginate are major components of biofilms formed by *P. aeruginosa* [234,235] and play significant roles in adhesion, determination of biofilm architecture, resistance to antibiotics and the host

Table 3
Novel therapies for inhibiting *Pseudomonas aeruginosa* biofilm.

Novel inhibitory agents	Mode of action/target	Reference
Antimicrobial peptides	Kill bacterial cells through both membranolytic and non-membranolytic mechanisms, and by interacting with intracellular targets, such as DNA, RNA, and proteins	LL-37 [236], Peptide 1037 [237], WLBU2 [238], P5 [239], Chensinin-1 [240]
Quorum sensing inhibitors	Signal molecule degradation, preventing accumulation of signal molecules and antagonism of the signals, Attenuation of virulence factors	Brominated furanones [171], meta-bromo-thiolactone [241], M64 [242], Itaconimides [243] 3-amino-7-chloro-2-nonylquinazolin-4 (3*H*)-one (ACNQ) [244], Silver nanoparticle with 4-nitropyridine N-oxide (4NPO) [245] quercetin [246]
Iron chelators	Chelation of the iron	desferrioxamine-gallium [186], N,N'-bis (2-hydroxybenzyl) ethylenediamine-N,N'-diacetic acid (HBED) [247] deferoxamine and deferasirox [192]
Enzymes	Exopolysaccharide	alginate lyases [248], glucanohydrolases (dextranase and mutanase) [249], glycoside hydrolase (PelAh and PslGH) [250], deoxyribonucleases (e.g., DNase I and Dnase1L2) [251,252]
Immunotherapy (Monoclonal antibodies)	Bacterial DNA-binding proteins	Monoclonal antibodies [253]
Gaseous agents	Dispersal of biofilm by modification of intracellular c-di-GMP levels	Nitric oxide [254]
Photodynamic therapy	Photoinactivation	Tetracationic porphyrin [5,10,15,20-tetrakis (1-methylpyridinium-4-yl)porphyrin tetra-iodide, Tetra-Py^{+}-Me] [255], GD11 [256]
Photothermal therapy	Generates localized heat resulting in irreversible damage to bacterial cells	Gold nanoparticles [257]
Herbal medicine	expression of biofilm-associated genes (*rhlR, rhlA* and *lasB*)	H. patriniae extract [258], Eiekikaryu S, Iribakuga and Hyakujunro [259]
Phage therapy	Lysis of cell membrane and wall	IME180 [260], vB_PaeM_SCUT-S1 and vB_PaeM_SCUT-S2 [261], Phage LKA1 O-specific polysaccharide lyase [262], Engineered T7 bacteriophage that encode lactonase enzyme [263]

defence mechanism. Polysaccharide Psl helps bacteria in adherence to a new surface, cell migration, and communication with other cells of the biofilm during its early stage of formation. Polysaccharide Psl protects cells against phagocytosis and oxidative stress during infection. Alginate protects biofilm bacteria from opsonophagocytosis, free radicles formed by immune cells and antibiotics [235]. Table 3 summarizes novel approaches to inhibit *P. aeruginosa* biofilm.

6. Conclusions

Infections due to antibiotic-resistant *P. aeruginosa* are steadily increasing worldwide. Antibiotic resistance will continue to be a challenge with *P. aeruginosa* because of its high intrinsic resistance and ability to acquire resistance to all classes of antibiotics. The scientific community is making progress in the fields of bioinformatics, microbial genomics, target identification and screening techniques to find new potential therapeutic targets and molecular mechanisms for persistence and antibiotic resistance in *P. aeruginosa*; however, the number of new antibiotics being developed has fallen sharply.

To combat antibiotic resistance, and to minimize its dissemination, there is an urgent requirement for novel anti-*Pseudomonas* therapies. Many novel therapeutic agents are under development and are mainly focused on a narrow spectrum, pathogen-specific, anti-virulence, and patient-specific approach. Novel alternative therapies like bacteriophage therapy, iron-chelating agents and immunotherapy have shown promising results *in vitro*, animal models and in human studies; however, there are still many difficulties and challenges before they can be applied in the clinic. Controlled clinical trials are necessary to prove their safety and efficacy before they are used for routine care. The approach of using combination of antibiotics with alternative therapies will be necessary to overcome the growing problem of resistance.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Available statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics statement

None.

Informed consent

None.

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