Pseudomonas aeruginosa: A review of their Pathogenesis and Prevalence in Clinical Settings and the Environment

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The genus Pseudomonas consists of more than 120 species that are ubiquitous in moist environments such as water and soil ecosystems and are pathogenic to animals and humans. Within the genus of Pseudomonas, P. aeruginosa is most frequently associated with human infections. The bacterium is regarded as an opportunistic pathogen, primarily causing nosocomial infections in immunocompromised patients. The existing knowledge regarding the pathogenesis of P. aeruginosa has mainly been obtained through studying clinical isolates; particularly those involved in causing chronic lung infection in cystic fibrosis patients. Nosocomial infections commonly associated with P. aeruginosa include ventilator-associated pneumonia, catheter-associated urinary tract infections, wound infections in severe burn patients and sepsicaemia with their pathogenesis shown to be multifactorial. The bacterium is also capable of producing a number of toxins via the type III secretion system, as well as secreting enzymes and proteins including elastase, phospholipase C and siderophores. However, P. aeruginosa is also a waterborne pathogen, commonly found in environmental waters as well as in other sources such as sewage treatment plants. The public health implication of these bacteria whilst in the environment has not been fully investigated. Here we review our present knowledge about the pathogenesis of P. aeruginosa in clinical settings and the environment.

Key words: Pseudomonas aeruginosa, Virulence factors, Pathogenesis

1. Background

Included in the category of genus Pseudomonas are genus Pseudomonas which contains more than 120 species that are all-over in moist environments such as water and soil ecosystems and infective to plants, animals and humans (1, 2). Pseudomonas species are easily detectable on agar due to the production of pigments such as pyoverdine which is a yellow-green, fluorescent pigment, and pyocyanin that is a blue-green pigment (3-6). Within the Pseudomonas species, P. aeruginosa is most frequently associated with causing human infection; however, it naturally exists in the environment (7, 8). The bacterium is regarded as an opportunistic pathogen, primarily causing nosocomial infections in immunocompromised patients (9-12). However, it is capable of causing a wide-spectrum of infections when normal physiological function is disrupted, including damaged epithelial barriers (13), depleted neutrophil production (14), altered mucociliary clearance (15) and the use of medical devices (16, 17). P. aeruginosa is rarely associated with causing chronic infections in previously healthy patients, although fatal cases of P. aeruginosa infections in previously healthy people have been reported (18, 19).

2. Context

2.1. P. aeruginosa causing respiratory tract infections

P. aeruginosa is well known for its ability to establish permanent residency in the airways of cystic fibrosis (CF) patients, resulting in the recurrence of chronic lung infections, progressive decline in lung function and increased morbidity and mortality rates (20, 21). The mechanism by which P. aeruginosa colonizes CF patients relies mainly on the pathogenesis of this genetically inherited lung disease. The disease is attributed to a gene mutation in cystic fibrosis transmembrane conductance regulator (CFTR) protein; a chloride channel which is involved in maintaining homeostasis in epithelial tissues (15, 22, 23). Dysfunction of CFTR channels disrupts the regulation of chloride ion transport across the epithelia, resulting in sodium hyperabsorption and impaired mucociliary clearance (15, 22, 23). Thick viscous mucus resides in the airways causing obstruction and blockages, and mucus hypoxia promotes P. aeruginosa colonization (24, 25). Non-CF patients are also susceptible to respiratory tract colonization of P. aeruginosa, especially patients with chronic obstructive pulmonary disease (COPD) (26). COPD patients display similar symptoms to CF patients such as decreased mucociliary clearance, and under these predisposing conditions P. aeruginosa is able to colonize and cause infection (15, 26).

P. aeruginosa is also a common causative agent of hospital-acquired pneumonia (HAP), in immunocompromised individuals (27). Colonization of the respiratory tract is initiated by the contamination of medical equipment and/or cross-colonization from other patients (27, 28). HAP is frequently acquired by patients using mechanical ventilation, termed ventilator-associated pneumonia (VAP) (29). P. aeruginosa is frequently isolated from hospital medical equipment, due to the bacterium’s ability to survive in biofilms (16, 30). Previous studies have associated VAP with prolonged use of ventilation and prolonged duration in intensive care units (ICU) (29).

2.2. P. aeruginosa causing urinary tract infections

Urinary tract infections (UTI) caused by P. aeruginosa usually occur secondary to catheterization, instrumentation or surgery. Catheterization of the urinary tract is the major cause of nosocomial acquired-UTI by P. aeruginosa (31). Catheters are utilized by pathogen as a source of host entry, attaching to the catheter surface in well-constructed biofilms (16, 17, 30). Furthermore, the insertion of the catheter may also disrupt mucosal epithelial layers, promoting bacterial colonization (31, 32).
2.3. *P. aeruginosa* causing skin and soft tissue infections

*P. aeruginosa* is the most commonly isolated bacterium colonizing severe burns and wound infections (33-35). Wound infections caused by multidrug resistant (MDR) *P. aeruginosa* have been associated with high morbidity and mortality rates worldwide (33, 35). Estabbanati and colleagues (2002) investigated *P. aeruginosa* isolated from burn wound infections in a burn centre in Tehran and found that the majority of isolates were MDR and less than half of the patients were discharged from the centre (34). Nosocomial outbreaks of *P. aeruginosa* have been reported in surgical wounds, causing post-operative wound infections (36, 37). In addition, *P. aeruginosa* can disseminate from the initial infection site and enter the bloodstream, causing septicemia (36). High mortality rates of *P. aeruginosa* septicemia have previously been reported (38, 39).

Mild skin infections can occur in previously healthy people, associated with *P. aeruginosa* contamination in swimming pools, hot tubs and other water sources (40-43). Follicular dermatitis caused by *P. aeruginosa* has previously been described as an itchy rash with a red base and white pustules (44). In addition, nail diseases (e.g. onycholysis) are susceptible to colonization of *P. aeruginosa*, and is commonly referred as “green nail syndrome” (45-47). Paronychial infection has been associated with prolonged exposure to moist environments (e.g. swimming). McNeil and colleagues (2001) investigated an outbreak of *P. aeruginosa* infections in post-surgical patients, reporting severe onycholysis and onychomycosis in a nurse’s thumbnail as the primary source (47).

2.4. *P. aeruginosa* causing bacterial keratitis

*P. aeruginosa* is the leading cause of bacterial keratitis (48), and occurs in patients with pre-existing ocular disease, in post-ocular surgery patients and in individuals who use contact lens. *P. aeruginosa* has been shown to adhere to the disrupted corneal epithelial cells, and internalize rapidly (49, 50). Contact-lens associated keratitis is mediated by the extended use of contact lens that has been shown to disrupt the epithelial surface of the cornea, causing cornea abrasions (49-51). Furthermore, bacterial keratitis initiated by contact lens contamination has been associated with patient noncompliance with appropriate contact lens care (52).

2.5. *P. aeruginosa* causing ‘swimmers ear’ infections

Otitis externa, commonly known as ‘swimmers ear’, is an inflammation or infection of the external auditory canal, due to prolonged exposure to moisture and/or the insertion of foreign objects (e.g. cotton tips) (53, 54). It is well known that *P. aeruginosa* is the most common pathogen of otitis externa, strongly associated with swimming in contaminated recreational pools (55).

2.6. Pathogenesis of *P. aeruginosa*

The pathogenesis of *P. aeruginosa* has been extensively studied and proven to be a multifactorial process, mediated by quorum sensing. *P. aeruginosa* possesses two quorum sensing systems, las and rhl that facilitate cell to cell communication through production of signalling molecules termed autoinducers to target specific receptors for activation (56-58). However, a high population density is necessary for the concentration of inducers to go beyond threshold. Maximal receptor activation induces gene expression of several virulence factors and biofilm formation (57-58). There are a number of virulence properties that help *P. aeruginosa* to colonize and evade the host’s immune system to cause infection, including adhesions, the type III secretion system and other secreted proteins.

2.7. Adhesions

Adhesion of bacteria to the host cell surface is the first step toward colonization and initiation of the disease (59). In *P. aeruginosa*, adhesion is mediated by type IV pili and the formation of biofilms (60-77). Type IV pili are the filamentous appendages attached to the cell surface of the bacterium. More than 40 genes involved in the biogenesis and function of type IV pili have been previously identified (60). Hahn and colleagues (61) have also shown that type IV pili accounted for 90% of the adherence, function and virulence in a mouse infection model. Type IV pili also assist in facilitating ‘wringing motility’; the retraction and extension of pili, to facilitate bacterial movement along the host cell surface (62-64). As a result, the surface movement assists in the formation of microcolonies, which develop into a mature biofilm (65-66).

*P. aeruginosa* also secretes extracellular polysaccharides; alginate, polysaccharide-encoding locus (pel) and polysaccharide synthesis locus (psl) that are also involved in forming the biofilm matrix embedded around microcolonies (68). Biofilms protect the bacterium from the host immune system components, as well as resistance to antibiotics (69). Alginate is commonly described as ‘slime’, that is commonly associated with sputum cultures from CF patients, suggesting that mucoid phenotypes of *P. aeruginosa* are important for persistence and establishing permanent residency in the lungs of CF patients (70). It has been previously shown that mucoid phenotypes interfere with antibiotic effectiveness by decreasing uptake (71). Alginate has also been shown to inhibit phagocytosis and scavenge free radicals (72, 73). However, non-mucoid phenotypes (alginate deficient) have the ability to form biofilms, by utilizing pel and psl (74, 75). A study by Ma et al. (76) has shown a decrease in binding to the airway epithelial cells in psl-mutant strains, suggesting psl is necessary for adhesion.

Previous studies have compared virulence and antibiotic-resistance profiles of mucoid (alginate producing) and non-mucoid (alginate deficient) biofilm phenotypes (74, 77). Mittal et al. (77) correlated biofilm-producing *P. aeruginosa* with increased renal tissue damage compared to non-mucoid phenotypes of *P. aeruginosa*, suggesting that the biofilm production contributes to the pathogenicity and host damage in *P. aeruginosa* urinary tract infections. In contrast, Wozniak et al. (74) studied antibiotic resistance profiles in wild-type and alginate-mutant biofilms and reported no differences in the antibiotic resistance.

In addition to type IV pili and biofilm formation, adhesion is also mediated by other various cell surface features, including lipopolysaccharides (LPS). LPS is a large molecule found on the outer surface membrane in most Gram-negative bacteria (78). The LPS structure is heterogeneous in its lipid structure, presenting in two glycoforms in *P. aeruginosa* (79). LPS serve as recognition molecules to the innate immune system, responsible of causing bacterial infection-induced inflammation (78, 79). The induced inflammatory response is variable, associated with the level of acylation in lipid A, whereby a fully hexa-acylated lipid A is necessary for a vigorous response (80). LPS signal transduction is a complex process mediated by binding LPS to lipopolysaccharide-binding protein (LBP) to form LPS-LBP complexes, that are transferred to CD14 receptors, for secondary activation of Toll-like receptor-4 (79, 80). Previous find-
ings have shown that initial isolation of *P. aeruginosa* from CF patients contain O-antigen, however upon establishment of chronic infection, the same strain of *P. aeruginosa* was found to be LPS O-antigen-deficient (81, 82).

### 2.8. Type III secretion system

*P. aeruginosa* interacts with the host via a protein, needle-like appendage known as the type III secretion system (T3SS). The T3SS injects toxic effector proteins into the cytosol of eukaryotic cells to inhibit cellular function for bacterial survival. Four effector toxins have been identified in *P. aeruginosa* and include exoenzymes S, T, U, and Y. ExoS and ExoT are bifunctional, possessing GAPase activating protein (GAP) activity and ADP-ribosyltransferase activity (84, 85), while ExOY is an adenylate cyclase (86). Previous studies have shown that ExoS, ExoT and ExoY function to acquire cytolitic activity, inhibiting epithelial cell invasion and preventing phagocytosis (86-88). Furthermore, these proteins are associated with disruption of endothelial cell junctions, via cell retraction and rounding to alter the cytoskeleton (86-88).

However, ExoU is a potent cytotoxin with phospholipase A2 (PLA2) activity; the ability to cleave phospholipid membranes to cause cell lysis (89, 90). ExoU has also been shown to acquire cytolitic activity to various cell types including epithelial cells, macrophages and fibroblasts (83, 89, 90). In addition, the PLA2 activity initiates inflammation due to the production of arachidonic acid for cyclooxygenase and lipoxygenase pathways, resulting in prostaglandins production (91).

Feltman and colleagues (92) have previously reported that *P. aeruginosa* isolates possess either exoS or exoU genes, not both. On the other hand, previous studies by Wolfgang et al.(93) have shown that this feature did not exist among clinical strains, concluding that all clinical isolates carried both exoS and exoU genes. A high prevalence of ExoS production has been documented in *P. aeruginosa* isolates from urinary tract and wound infections (92, 94). Conversely, ExoU has reported to be highly associated in Pseudomonal lung infections, including hospital-acquired pneumonia (85, 95). In fact, it has been shown that a significant reduction in lung pathology and virulence is associated with ExoU deletion in mutated isolates (96). Consistently, ExoU production in animal models and in patients has been strongly associated with the acceleration of lung injury (89, 97-99). In contrast, Dacheux and colleagues (99) associated CF isolates with a low prevalence of ExoU (i.e. 10%), which is similar to the study by Feltman and colleagues (92), who found that ExoU in only found in 8% of CF isolates. This suggests that virulence properties of *P. aeruginosa* causing lung infections i.e. pneumonia are dissimilar to lung infections associated with CF patients. Previous studies have suggested that ExoT is a non-variable virulence property, which is prevalent in all clinical isolates of *P. aeruginosa* (92, 100). In addition, Feltman and colleagues (92) also reported ExoY to be present in most clinical isolates of *P. aeruginosa*, supporting a similar finding by Dacheux and colleagues (99).

### 2.9. Other secreted virulence properties of *P. aeruginosa*

*P. aeruginosa* secretes a haemolytic and a non-haemolytic phospholipase C (PLC). Studies have shown that non-haemolytic PLC has no pathogenic activity, whereas haemolytic PLC degrades phosphatidylcholine and sphingomyelin that are commonly found within eukaryotic membranes and host lung surfactant, principally to cause lung injury (101, 102). Additionally, Meyers et al (102) also reported that inactive forms of PLC were unable to cause an inflammatory effect. In addition, *P. aeruginosa* secretes elastase (LasB); a metalloprotease involved in the host colonization and tissue damage (103). Previous studies have suggested LasB as an important virulence factor for bacterial survival from the host immune system, through degradation elastin and collagen (103), immune components including cytokines, chemokines, IL-2 and IL-8 and inactivation of immunoglobulin A and G (104, 105). Previous studies have shown a high prevalence of the lasB gene in *P. aeruginosa*, irrespective of their isolation origin (106-108).

*P. aeruginosa* secretes yellow-green fluorescent pigment known as pyoverdin (4), that functions as a siderophore to acquire and transport iron from the environment through specific protein receptors on the outer membrane (109, 110). Three types of pyoverdines have been identified, although each strain of *P. aeruginosa* produces only one type (109). Animal models have suggested that pyoverdin is a virulence-associated factor aspynodin-deficient mutants demonstrate no virulence (110). A variety of phenazines are also secreted by *P. aeruginosa*, including pyocyanin. Pyocyanin is a blue reduct-active secondary metabolite that is responsible for the production of a blue-green pigment, commonly used in rapid diagnosis of *P. aeruginosa* (111-112). Previous studies have suggested that pyocyanin is a major virulence factor, interfering with numerous cell functions (112).

### 2.10. Antibiotic resistance in *P. aeruginosa*

Antibiotic resistant (AR-*P. aeruginosa* are strongly associated with nosocomial infections, that are a worldwide health concern due to the increasing development of MDR strains (i.e. resistance to at least three antibiotics). Various therapeutic challenges exist with MDR *P. aeruginosa* due to the limit of effective treatment strategies. Current literature is strongly associated inadequate empirical treatment with increased rates of mortality and morbidity (113-114). *P. aeruginosa* is intrinsically resistant to various antibiotics due to a low permeability in the outer membrane, which acts as a selective barrier (115, 116). However, this bacterium is a highly diverse pathogen that is capable of adaptation to the surrounding environment. When subjected to antibiotic selective pressure, the induced response facilitates bacterial survival and develops antibiotic resistance (115). The emergence of antibiotic resistance has been reported during host colonization of CF patients, whereby *P. aeruginosa* strains develop and acquire resistance during antimicrobial therapy (117). Studies by Messadi and colleagues (118) have reported a strong correlation between increased use of ciprofloxacin with increased prevalence of ciprofloxacin resistant strains. Therefore, another factor associated with the increase in MDR-*P. aeruginosa* is due to the frequent use of antimicrobial agents.

In addition, these bacteria utilize different mechanisms to resist antibiotics, although the presence of a mechanism does not always justify the source of resistance (113, 117). Therefore, many researchers have suggested that a variety of mechanisms are involved including the production of inactivating enzymes, target site modification, utilisation of efflux pumps and chromosomal mutations (119). *P. aeruginosa* produces β-lactamases; enzymes that hydrolyze the peptide bond of the β-lactam ring to inactivate the antibiotics (120). *P. aeruginosa* is able to produce various β-lactamases, including extended-spectrum β-lactamases (ESBL), metallo-β-lactamases (MBL) and chromosomal cephalosporinase (AmpC).
Various types of MBLs have been described previously and are carried on integrons (121). Previous studies have reported that MBL-producing *P. aeruginosa* in blood stream infections are associated with high morbidity and mortality rates (122). AmpC differs to the other β-lactamases for the fact that the ampC gene is present in all strains of *P. aeruginosa*, although it requires a gene mutation, to cause hyper production and resistance (123).

Carbapenems are commonly used to treat *P. aeruginosa* infections due to their effectiveness against β-lactamase producing *P. aeruginosa*. An increased prevalence of carbapenem-resistant *P. aeruginosa* has been reported in hospitals worldwide (124, 125). A study conducted between 1996 and 2003 in a United Kingdom medical centre has reported the prevalence of imipenem resistant-*P. aeruginosa* increasing from 2% to over 40%, with the majority of the isolates belonging to a single clone (125). Similarly, Vitkauskieni and co-workers (126) studied the prevalence of carbapenem-resistant *P. aeruginosa* over five years at a tertiary university hospital and showed an increase of 53% to 88% of carbapenem-resistant *P. aeruginosa*. In addition, OprD is a specialised porin located in the outer membrane of *P. aeruginosa* that facilitates the influx of amino acids, peptides and imipenem (a carbapenem antibiotic). Conformational changes in the external loops 2 and 3 of OprD have been shown to inhibit imipenem entrance into the bacterium (127).

*P. aeruginosa* is also capable of acquiring resistance through mutation in specific chromosomal genes (115). Fluoroquinolone resistance is acquired by modifying type II topoisomerases; DNA gyrase (gyrA gene) and topoisomerase IV (parC gene), to inhibit antibiotic binding (128, 129). Previous studies have suggested that the first target for fluoroquinolones activity is DNA gyrase, followed by topoisomerase IV as the secondary target (129). However, Salma and colleagues (130) have reported quinolone-resistant *P. aeruginosa* isolates without mutations in gyrA and parC genes, suggesting that another resistance mechanism is also used for the acquisition of fluoroquinolone resistance, such as efflux pumps. Efflux pumps rapidly remove toxic substances (e.g. antibiotics) out of the cytoplasm as a result of hyper expression of the MexR efflux gene (131, 132). The efflux pumps are a three component system; the outer membrane protein, the energy-dependant pump and a linker protein (132). In *P. aeruginosa*, four different efflux systems belong to the resistance-nodulation-division (RND) family including MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY-OprM (132). Studies have shown a wide-spectrum of substrates specificity for each efflux pump, including β-lactams and fluoroquinolones for MexAB-OprM and MexCD-OprJ (133). Current literature suggests that the overexpression of one or more Mex pumps is associated with MDR-*P. aeruginosa* in clinical settings (131-133).

2.11. *P. aeruginosa* in the environment

*P. aeruginosa* as a waterborne pathogen is a growing concern to public health sectors. Many sources of environmental water could potentially be acting as a reservoir for potentially pathogenic strains of *P. aeruginosa* (8, 41). Various studies have shown that water resources (including sewage treatment plants and river water) are highly polluted with pathogenic bacteria including *P. aeruginosa* (134, 135). Public recreational swimming pools have also shown *P. aeruginosa* contamination (136-138). In addition, outbreaks of whirlpool-associated folliculitis and UTI have previously been reported (139, 140). Grobe and colleagues (137) showed mucoid phenotypes (possessing alginate) were able to survive in chlorinated water better than non-mucoid phenotypes. Despite this, non-mucoid strains of *P. aeruginosa* exist in swimming pool water (106). The presence of *P. aeruginosa* in swimming pools is associated with public health risks. Many studies have associated otitis externa, dermatitis, folliculitis and chloronychia with the use of swimming pools and hot tubs (141).

Lutz and Lee (142) studied the prevalence of antibiotic resistant *P. aeruginosa* in various swimming pools and hot tubs. These researchers found 96% of their isolates to be MDR including resistance to amikacin, aztreonam, gentamicin, ticarcillin/clavulanic acid and trimethoprim/sulfamethoxazole (142). In contrast, Tirominos and colleagues (42) isolated *P. aeruginosa* from hydrotherapy pools that have only shown 20% resistance to these antibiotics. It is generally accepted that the environmental strains of Pseudomonas show very little resistance to antibiotics however this assumption has not been fully verified. One major source of antibiotic resistant *P. aeruginosa* in the environment is the untreated hospital wastewater (UHWW). It has been shown that *P. aeruginosa* strains isolated from UHWW are commonly resistant to a number of antibiotics (3, 143). For instance, Fentefria and colleagues (143) compared *P. aeruginosa* strains isolated from UHWW and surface waters and showed a higher prevalence of MDR *P. aeruginosa* in the UHWW than the surface water.

*P. aeruginosa* is also an inhabitant of soil that can be pathogenic to plants (144). Pitondo-Silva and colleagues (145) isolated *P. aeruginosa* from soil of different crops. These researchers found the majority of isolates to be resistant to aztreonam and Ticarcillin that are commonly used in the treatment of *P. aeruginosa* in CF patients (145). Thus, Wolfgang et al. (93) compared the genome content of *P. aeruginosa* isolates from clinical and environment sources’ and concluded that gene conservation exists for *P. aeruginosa*.

2.12. Genetic diversity of *P. aeruginosa*

The complete genome of *P. aeruginosa* has been sequenced by Stover et al (147), reporting a genome size of 6, 262, 403 base pairs, which suggests that *P. aeruginosa* has the largest genomes amongst bacteria, with an estimated 5570 open reading frames (ORF). Of these ORF, 372 have been defined as functional genes, encoding proteins involved in cell adhesion and motility (e.g. type IV pili and exopolysaccharides), virulence factors (e.g. exoenzymes and the type III secretion system), LPS synthesis enzymes and other secreted proteins involved in the pathogenesis as described above. Other genes expressed in *P. aeruginosa*, are encoded for regulatory networks and outer membrane proteins (e.g. OprDporin family) and efflux systems for antibiotic resistance. Current literature suggests that the large genome size and genome complexity are responsible for the ability of this bacterium to adapt and thrive in a diverse range of environments (93). This high diversity has also resulted in the presence of large clonal groups of these bacteria in the environment.

Various genotypic typing methods are commonly used to identify persistent clones of these bacteria in clinical settings or the environment. Tielen and colleagues (148) have shown that *P. aeruginosa* strains isolated from UTI and catheter-associated UTIs are highly heterogeneous. Interestingly, these researchers found that some of their strains were closely related to *P. aeruginosa* clone C; which is a worldwide clone frequently isolated from the lung of CF patients (148). In a recent study, Naicker (135) examined the prevalence of Gram-
negative bacteria including P. aeruginosa in UHWW and their transition to a receiving STP and survival through its treatment processes. The results showed P. aeruginosa in UHWW were genetically distinct, although some strains were present at different times in the STP. Despite these findings, some researchers have observed that environmental strains of P. aeruginosa are genotypically and functionally equivalent to those isolated from clinical infections (7, 93, 147).

3. Conclusion
Hospitals and healthcare settings are regarded as reservoirs for large numbers of pathogenic Pseudomonas strains. Wastewaters from hospitals may contain a large number of these bacteria some of which can also be MDR. Recent studies on the prevalence of P. aeruginosa in UHWW and their dissemination in the environment suggest that certain clonal groups of these bacteria have the ability to survive transmission to the STPs and then through to the finally treated effluent before being released into surface waters. The presence and persistence of these bacteria in environmental waters may pose a great risk to the public health and requires further work to fully characterize and quantify the input of MDR P. aeruginosa strains from the hospitals compared with those originating from the general community or other wastewater-related sources.

Conflict of Interests
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