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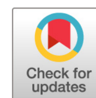

Advances in the Microbiology of *Stenotrophomonas maltophilia*

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SUMMARY *Stenotrophomonas maltophilia* is an opportunistic pathogen of significant concern to susceptible patient populations. This pathogen can cause nosocomial and community-acquired respiratory and bloodstream infections and various other infections in humans. Sources include water, plant rhizospheres, animals, and foods. Studies of the genetic heterogeneity of *S. maltophilia* strains have identified several new genogroups and suggested adaptation of this pathogen to its habitats. The mechanisms used by *S. maltophilia* during pathogenesis continue to be uncovered and explored. *S. maltophilia* virulence factors include use of motility, biofilm formation, iron acquisition mechanisms, outer membrane components, protein secretion systems, extracellular enzymes, and antimicrobial resistance mechanisms. *S. maltophilia* is intrinsically drug resistant to an array of different antibiotics and uses a broad arsenal to protect itself against antimicrobials. Surveillance studies have recorded increases in drug resistance for *S. maltophilia*, prompting new strategies to be developed against this opportunist. The interactions of this environmental bacterium with other microorganisms are being elucidated. *S. maltophilia* and its products have applications in biotechnology, including agriculture, biocontrol, and bioremediation.

KEYWORDS *Stenotrophomonas*, antimicrobial agents, antimicrobial resistance, biofilms, biotechnology, cystic fibrosis, genomes, *S. maltophilia*, pathogenesis, risk factors

INTRODUCTION

Gram-negative drug-resistant bacteria are of significant concern for clinicians worldwide. The ability of these microorganisms to exchange and acquire antimicrobial resistance has contributed to the emergence of multidrug-resistant pathogens. The antimicrobial resistance surveillance programs monitoring these pathogens have discerned troubling upward trends in resistance. Genomic sequencing and analyses have enabled the epidemiological tracing of pathogens of significant virulence. Research has focused on unearthing the molecular mechanisms used by these organisms during infection and disease. A deeper understanding of these mechanisms has contributed to the discovery of novel antimicrobials against these pathogens.

The World Health Organization currently lists *Stenotrophomonas maltophilia* as an important Gram-negative multidrug-resistant bacterial pathogen in hospitals (https://www.who.int/drugresistance/AMR_Importance/en/). Infections by this environmental and opportunistic intrinsically drug-resistant organism are of significant concern among the immunocompromised patient population and can be fatal (1).

This pathogen has certainly made an impact on human health worldwide. *S. maltophilia* was one of the top six pathogens isolated from pneumonia patients in U.S. intensive care units (ICUs) during 2015 to 2017 (2), among the top 10 pathogens causing pneumonia in patients in Latin American medical centers during 2008 to 2010 (3), and ranked in the top 10 pathogens most frequently isolated from hospitalized pneumonia patients during 2009 to 2012, in which a high prevalence (4.4% in the United States and 3.2% in Europe and the Mediterranean) of this pathogen was noted (4). In an antimicrobial surveillance program during 1997 to 2016, the majority (62.6%) of the *S. maltophilia* isolates recovered from the Asia-Pacific region were from hospitalized pneumonia patients (5), and from 2003 to 2010, *S. maltophilia* was among the top four pathogens associated with intraabdominal infections (6).

As few new antimicrobials are available to treat this intrinsically drug-resistant human opportunist, there is a critical need to understand the interactions of *S. maltophilia* with its environment and develop new intervention strategies (7). This current

review will address advances in the study of the biology of *S. maltophilia* since the author's previous review (1).

CLINICAL SIGNIFICANCE AND MICROBIOLOGY

Stenotrophomonas maltophilia is an opportunistic pathogen with low virulence that causes a variety of human infections. *S. maltophilia* is associated with significant crude mortality rates as high as 69% in bacteremia patients (8, 9). Nosocomial and community acquisition of this pathogen is possible (1). This bacterium is an environmental organism that was originally named in 1943 as *Bacterium bookeri*, then *Pseudomonas maltophilia*, then *Xanthomonas maltophilia*, and finally classified as *Stenotrophomonas maltophilia* (10–16). A detailed description of its growth requirements is found in the author's previous review of *S. maltophilia* (1). While *S. maltophilia* is characterized as oxidase negative, oxidase-positive strains of this pathogen have been identified (17, 18). This microorganism is associated with plant rhizosphere and is important for elemental cycling of sulfur and nitrogen, while as a human opportunist, it may be a participant in polymicrobial infections (19).

S. maltophilia Infections and Risk Factors

S. maltophilia-associated human infections include bacteremia (20–44), respiratory infections (20, 22, 26, 28, 30, 32, 38, 40, 43–76), eye infections (38, 40, 77–96), endocarditis (97–100), nervous system and spinal cord infections (28, 101–105), gastrointestinal tract infections (26, 28, 40, 43, 44, 106–109), liver infection (85), urinary tract infections (20, 28, 40, 43, 44), soft tissue and bone infections (20, 22, 28, 40, 43, 44, 63, 110–123), and medical implant infections (40, 43, 44, 99, 124–128) (Table 1). Rare *S. maltophilia*-associated infections have been observed, including keratitis in patients with bandage contact lens (82), osteomyelitis from *S. maltophilia* following an open distal tibial fracture (113), death from neutropenic enterocolitis (106), oral cavity lesions (109), and stomatitis (118). A recent review addresses the management of *S. maltophilia* infection of skin and soft tissues (117). *S. maltophilia* is able to grow in various bodily fluids; recently, this pathogen was observed to grow in bronchial secretions following bronchoscopic valve implantation (129). This pathogen can be recovered from cystic fibrosis (CF) patients' airways and sputa (60, 67).

The identification of risk factors for *S. maltophilia* infection may provide insights for the proactive prevention of *S. maltophilia*-associated disease in patients. Determining the risk of infection requires one to consider several factors, including the immune system of the patient, underlying malignancies, structural abnormalities, and the virulence of the pathogen. Common risk factors associated with mortality in *S. maltophilia* bacteremia patients (with or without a hematological disorder) identified by univariate analyses include septic shock (21, 23, 29, 42), ventilation (23, 29, 32, 39), and ICU admission/length of hospital stay (29, 32, 39, 42), and those identified by multivariate analyses include an elevated sequential organ failure assessment (SOFA) score (29, 32) (Table 2). Multivariate analysis of patients with *S. maltophilia* bacteremia identified hypoalbuminemia, hematologic malignancy, quinolone-resistant *S. maltophilia*, septic shock, and prior chemotherapy as risk factors for mortality (31, 42) (Table 2). Multivariate analysis of patients with hematological disorders and *S. maltophilia* bacteremia identified inadequate initial antimicrobial treatment, respiratory failure, nonremission posttreatment for primary diseases, pneumonia, and elevated SOFA score as risk factors for mortality (21, 32) (Table 2). A recent study of *S. maltophilia* bacteremia patients identified risk factors for 30-day mortality that included anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drug use and high levels of aspartate aminotransferase, lactate dehydrogenase, and C-reactive protein (27).

Risk factors for mortality in hospitalized patients with *S. maltophilia* infections commonly identified by univariate analyses include ICU stay (22, 28, 40), central venous or urinary catheter use (22, 28, 40), prior antibiotic use (22, 28, 40), and mechanical ventilation (22, 28), and those identified by multivariate analyses include ICU stay (22, 40) (Table 2).

TABLE 1 *S. maltophilia* associated infections

Organ/body part	Infection	Reference(s)
Blood	Bacteremia	20–44
Respiratory tract	Pneumonia, ventilator-associated pneumonia, respiratory infection	20, 22, 26, 28, 30, 32, 38, 40, 43, 44, 53, 55, 57, 59, 62–64, 68, 70, 71, 76
	Bronchiectasis	61
	Acute and chronic CF infection	45–52, 54, 56, 58, 60, 65–67, 69, 72–75
Eye	Endophthalmitis	77–81, 85, 86, 95
	Keratitis	82–84, 89–92, 94, 96
	Cornea	40, 88
	Conjunctival ulcer, conjunctivitis	38, 87
	Dacryocystitis	93
Heart	Endocarditis	97–100
Nervous system and spinal cord	Meningitis, cerebrospinal fluid	28, 102, 103
	Discitis	101, 105
	Brain abscess	104
Gastrointestinal tract	Enterocolitis, gastrointestinal infection	26, 28, 43, 44, 106
	Intraabdominal abscess	107
	Peritonitis	40, 108
	Oral cavity	109
Liver	Hepatic abscess	85
Urinary tract		20, 28, 40, 43, 44
Soft tissue and bone	Skin and tissue	20, 22, 28, 40, 43, 44, 63, 111, 112, 115–120, 122, 123
	Arthritis	114
	Osteomyelitis	110, 113, 121
Implants	Catheter	40, 43, 44, 124, 126–128
	Ventriculoperitoneal shunt infection	125
	Cardioverter defibrillator lead	99

Common risk factors associated with developing *S. maltophilia* infection identified by univariate analyses include invasive procedures such as ventilation (33, 38, 71) and antibiotic use (33, 38, 71), and those identified by multivariate analyses include antibiotic use (24, 33, 57, 61), invasive procedures in neonates and infants <1 year old (38, 71), and ICU stay for pediatric patients (24, 71) (Table 3). In a retrospective study (2014 to 2016), univariate analysis identified patients 0 to 5 years of age as being at risk for *S. maltophilia* nosocomial bloodstream infections (41) (Table 3).

The judicial use of antibiotics used to treat *S. maltophilia* infections is important. The potential for *S. maltophilia* infection in bacteremia and cardiovascular patients receiving broad-spectrum antibiotics should be considered (20, 26). Hematologic malignancy, thrombocytopenia, and previous quinolone use within 30 days have been suggested as possible risk factors for hemorrhagic pneumonia in *S. maltophilia* bacteremia patients (30).

The challenge of treating pneumonia patients with *S. maltophilia* is significant. In comparison to the number of studies of risk factors identified for *S. maltophilia* bacteremia, only a few studies report the risk factors for *S. maltophilia* pneumonia. Mortality risk factors reported for *S. maltophilia* ventilator-associated pneumonia include age and chronic heart failure (57). Risk factors for *S. maltophilia* pneumonia in ICU patients were identified as higher SOFA score and immunosuppression (130). Computed tomography findings of patients reveal differences between immunocompromised and immunocompetent patients with *S. maltophilia* pneumonia, with patchy ground glass opacities observed in patient lungs (59). Treatments of patients with *S. maltophilia* pneumonia have indicated no difference between efficacy of trimethoprim-sulfamethoxazole (TMP-SMX) or levofloxacin treatment (62) and that delay of adequate antimicrobial treatment and

TABLE 2 Risk factors associated with *S. maltophilia* mortality

Infection	Risk factor(s): Univariate or bivariate analysis	Risk factor(s): Multivariate analysis	Reference
Mortality in patients with bacteremia	Elevated Charlson or SOFA score, septic shock, ICU stay, mechanical ventilation, continuous renal replacement therapy, urethral catheter or drainage tube	Elevated SOFA score	29
	Septic shock, mechanical ventilation, central venous catheter, hemodialysis	NA[a]	23
	ICU admission, ventilation	NA	39
	NA	Hypoalbuminemia, hematologic malignancy, quinolone-resistant *S. maltophilia* strains	31
	Length of hospital stay, nosocomial source of infection, septic shock, prior chemotherapy, prior carbapenem use	Septic shock; prior chemotherapy	42
Mortality in patients with hematologic malignancy and *S. maltophilia* bacteremia	Old age, length of hospital stay, polymicrobial infection, prior *S. maltophilia* isolation, underlying malignancy (refractory or recurrent), Charlson comorbidity index (CCI) ≥3, prior ICU stay, mechanical ventilation, renal replacement therapy, elevated SOFA score, no. of prior antibiotics used	Hemorrhagic pneumonia, nonhemorrhagic pneumonia, elevated SOFA score	32
	Catheter reimplantation, accompanying polymicrobial infection, APACHE II score, temp >39°C; septic shock, respiratory failure, inadequate initial antimicrobial treatment, nonremission posttreatment for primary diseases	Inadequate initial antimicrobial treatment, respiratory failure, nonremission posttreatment for primary diseases	21
Mortality in hospitalized patients with *S. maltophilia* infections	ICU stay, mechanical ventilation, catheter (central venous, urinary), prior antibiotic use	ICU stay, mechanical ventilation, catheter (central venous, urinary), prior antibiotic use	22
	ICU stay, catheter (central venous, urinary, other), elevated white blood cell count, coisolation of another Gram-negative pathogen, empirical use of tigecycline, targeted therapy use of colistin, tigecycline, and TMP-SMX	ICU stay	40
	Arterial hypertension, type 2 diabetes, acute myocardial infarction, leukemia, urinary catheter, central venous catheter, mechanical ventilation, hemodialysis or peritoneal dialysis, cardiac arrest, length of hospital stay, ICU stay, use of corticosteroids, antifungals, vasopressors, vancomycin, and TMP-SMX	NA	28

[a]NA, not available.

combination antimicrobial therapy has no significant effect on mortality (55). No difference in patient outcome was reported for patients treated with TMP-SMX and untreated patients in a small study of tracheostomy-dependent pediatric patients with *S. maltophilia* respiratory infection (70). A higher mortality rate has been reported for pneumonia patients coinfected with *Pseudomonas aeruginosa* and *S. maltophilia* (76). Both of these pathogens are biofilm formers in the respiratory tract, and biofilm infections with multidrug-resistant pathogens such as these are notoriously difficult to treat therapeutically. There is an urgent need to develop more effective strategies to treat these mixed-culture infections.

Acquisition of TMP-SMX- and levofloxacin-resistant *S. maltophilia* in patients is of concern. Multivariate analyses have identified risk factors for infection by TMP-SMX-resistant *S. maltophilia*, including previous fluoroquinolone use (43) and prolonged hospitalization (28) (Table 3). Previous fluoroquinolone use has been identified through multivariate analysis as a risk factor for infection by levofloxacin-resistant *S. maltophilia* (44) (Table 3). A recent report of an adverse drug effect resulting from levofloxacin treatment of a neonate with *S. maltophilia* highlights the necessary monitoring of neonates receiving drug therapy; in this report, levofloxacin was suggested to cause

TABLE 3 Risk factors associated with developing *S. maltophilia* infection or acquisition of drug-resistant *S. maltophilia*

Infection	Risk factor(s)		Reference
	Univariate or bivariate analysis	Multivariate analysis	
S. maltophilia bacteremia in pediatric patients	NA[a]	Prior use of carbapenems, prior ICU stay	24
Ventilator-associated pneumonia due to *S. maltophilia*	Hematological organ failure, shock, female gender	SOFA score >2 (respiratory and coagulation), prior antibiotic use (uredio/carboxypenicillin, carbapenems)	57
S. maltophilia bacteremia in patients with hematologic malignancy	Length of hospital stay, polymicrobial infection, previous *S. maltophilia* isolation, breakthrough bacteremia during carbapenem therapy, UTI, pneumonia, leukemia, allogenic stem cell transplantation, elevated SOFA score, mechanical ventilation, prior antibiotic use (including TMP-SMX)	Polymicrobial infection, previous *S. maltophilia* isolation, prior antibiotic use (including TMP-SMX), breakthrough bacteremia during carbapenem therapy	33
Nosocomial bloodstream infection with *S. maltophilia*	Patient age (0–5 yrs)	NA	41
Acquisition of *S. maltophilia* in patients with non-CF bronchiectasis	NA	For single *S. maltophilia* isolation: lower baseline % predicted FEV_1 ≥3 lobes or cystic bronchiectasis on computed tomography; for chronic *S. maltophilia* isolation: no. of courses of intravenous antibiotics before and after *S. maltophilia* isolation; absence of *P. aeruginosa* chronic isolation	61
Severe *S. maltophilia* infection in pediatric patients (mainly newborns and infants <1 yr old)	Invasive procedures, mechanical ventilation, ICU admission within prior 30 days, prior use of carbapenems	Invasive procedures, mechanical ventilation, ICU admission within prior 30 days	71
S. maltophilia infection in neonates	Invasive procedures (mechanical ventilation, urinary catheter), use of aminoglycoside and carbapenem, total parenteral nutrition, histamine 2 blockers, exposure to steroids, cholestasis, length of hospital stay	Invasive procedures, length of hospital stay	38
Acquisition of TMP-SMX-resistant *S. maltophilia*	Bivariable analysis: prior exposure to fluoroquinolones, length of ICU stay, length of hospital stay	Prior exposure to fluoroquinolones	43
	Gastrostomy or jejunostomy, tracheostomy, length of hospital stay, lumbar puncture	Length of hospital stay	28
Acquisition of levofloxacin-resistant *S. maltophilia*	Bivariable analysis of levofloxacin-resistant *S. maltophilia* infected compared with levofloxacin-sensitive *S. maltophilia* infected: exposure to fluoroquinolones	Previous use of fluoroquinolones	44
	Bivariable analysis of levofloxacin-resistant *S. maltophilia* infected compared with patients without *S. maltophilia*: prior ICU stay, prior exposure to antibiotics (4th generation cephalosporins, carbapenems, glycopeptides, fluoroquinolones), no. of different antibiotic classes in prior exposure, previous indwelling devices (central venous catheter, urinary catheter, ventilation, nasogastric tube)	Previous use of fluoroquinolones, recent ICU stay, no. of different antibiotic classes in prior exposure	44
Predicting factors for *S. maltophilia* bacteremia with quinolone-resistant strains	High Charlson score, length of hospital stay prior to bacteremia, central venous catheter, Foley catheter, mechanical ventilator	High Charlson score, central venous catheter	31

[a]NA, not available.

hyperbilirubinemia (540). In summary, these studies underscore the importance of careful administration of antibiotics to treat *S. maltophilia* infections.

TMP-SMX and fluoroquinolones continue to show good efficacy against *S. maltophilia*. As an example, a recent study of military trauma patients infected with *S.*

maltophilia demonstrated that *S. maltophilia* isolates were susceptible to TMP-SMX (99%), minocycline (100%), and moxifloxacin (97%) (63). Serial isolates remained susceptible to TMP-SMX (81%) and minocycline (100%) (63).

S. maltophilia is associated with a specific host immune response, compromised lung function (51, 73, 74), and has been suggested as an indicator of CF lung disease severity (46). Acute and chronic *S. maltophilia* infections in CF patients have been studied (45–52, 54, 56, 58, 60, 65–67, 69, 72–75). This pathogen can be a cocolonizer in the lungs of CF patients, where it demonstrates genetic variability and adaptability to this habitat. Guidelines for infection prevention in CF patients recognize the possible transmission of aerosol particles containing *S. maltophilia* and recommend the use of masks by CF patients within health care settings and the design of negative-pressure rooms within patient care institutions (131, 132).

No seasonal pattern of acquisition has been noted for *S. maltophilia* in U.S. CF pediatric patients (66). No significant difference has been observed for the presence of *Stenotrophomonas* in lung microbiota across CF patient age groups (48). Data from the U.S. CF Foundation patient registry during 2003 to 2011 and 2006 to 2012 and from the European CF Society patient registry during 2011 to 2016 have indicated that the prevalence of *S. maltophilia* has increased over time (54, 56, 67).

Recent studies have examined risk factors for *S. maltophilia* infection and loss of lung function in CF patients (45, 49, 58, 69). Data analysis of the Toronto CF database (1997 to 2008) indicated that a steeper rate of median forced expiratory volume in 1 s (FEV_1) decline was associated with a significant risk for *S. maltophilia* infection (69). Acquisition of this pathogen has been linked to an increase in lung function deterioration in patients with chronic *S. maltophilia* infection (45).

In young CF patients, the isolation of *S. maltophilia* during the baseline year has been identified as a risk factor for higher rate of FEV_1 deterioration, along with high FEV_1, $\geq$1 pulmonary exacerbation, frequent/productive cough, and a low body mass index (BMI) (49). In CF patients with chronic *S. aureus* infection, one of the risk factors for lung function decline identified was coinfection with *S. maltophilia* (58).

S. maltophilia is not simply a colonizer but is an independent pathogen that causes infection. The occurrence of *S. maltophilia* infection in immunocompetent individuals is rare (59) and is more likely to occur among immunocompromised individuals. In both acute and chronic *S. maltophilia* infections, host immune responses are induced (73, 75, 133). In a mouse model of acute *S. maltophilia* lung infection, mice infected with a clinical CF *S. maltophilia* strain exhibited significant weight loss, greater invasion of the spleens, and damage of the lungs and displayed significantly higher cytokine (pulmonary tumor necrosis factor alpha [TNF-α], gamma interferon [IFN-γ], interleukin 6 [IL-6], and macrophage inflammatory protein 2 [MIP-2]) levels than mice infected with an environmental *S. maltophilia* strain (133). Chronic *S. maltophilia* infection results in a specific immune response in which significantly greater antibody levels against *S. maltophilia* flagellin and whole cells are observed than in patients with intermittent or no *S. maltophilia* infection (73). The levels of antibody against flagellin have been found to inversely correlate with FEV_1 percent predicted. In another study of patients with chronic *S. maltophilia* infection during 2008 to 2014, higher antibody levels were observed and associated with increased risk of pulmonary exacerbation (75). In respiratory coinfections of BALB/cJ mice with *S. maltophilia* (either K279a or a chronic CF sputum strain) and *P. aeruginosa*, mice exhibited significantly higher histological damage, higher numbers of immune cells and neutrophils, higher levels of TNF-α, IL-1α, IL-1β, and IL-6, and greater weight loss during infection than in uninfected mice (60). Together, these studies highlight the findings that both the humoral and cellular host immune responses are activated by *S. maltophilia* infection.

A study of antibiotic susceptibility of nonfermenting Gram-negative pathogens in CF patient respiratory samples from Spain, Northern Ireland, The Netherlands, United States, and Australia showed that co-trimoxazole is the preferred treatment for *S. maltophilia* infection; however, rates of resistance to this antimicrobial continue to rise

among CF patients (52). The emergence of antibiotic-resistant bacterial pathogens remains a significant concern for CF patients, particularly in countries where self-treatment is prevalent (134). These studies underscore the need for carefully considered use of antibiotics via prescription.

In CF patients with chronic *S. maltophilia* infection, their FEV_1 levels may not change significantly across the years, and the decline in FEV_1 may initiate prior to the patient presenting infection (50). Infection with chronic *S. maltophilia* infection is significantly associated with lung transplantation or mortality in comparison to that for infection with intermittent *S. maltophilia* (72).

Taken together, these studies illustrate the impact of *S. maltophilia* infection in CF patient populations. The CF patient with *S. maltophilia* infection is challenged through the specific immune response raised to the opportunist, the drug resistance of the pathogen, and deterioration of lung function.

Sources

Identification of sources of *S. maltophilia* in the clinical and community settings is an important step toward the prevention of infection of susceptible individuals. *S. maltophilia* has been recovered from surfaces, including invasive devices (124), a positive expiratory pressure therapy device (135), catheters (126, 128), endoscopes (136, 137), a hemodialyzer (127), water (138, 139), hydrotherapy equipment (140), ventilators (141), heater-cooler units (142), kitchen ICU tubing (143), dental biofilm (144), a contact lens storage case (145), and in hospital air (146). *S. maltophilia* has been isolated from food and beverages and equipment used for their preparation (147–159), a dishwasher seal (160), water sources (161–174), a contact lens storage case (145), dental biofilm (144), manure (175), and soil (176–178) (Table 4).

Drug-resistant *S. maltophilia* has been recovered from foods, including edible ice (151, 156), ready-to-eat street foods (155), fresh vegetables (147, 150, 153, 154), and cheeses (149, 157, 158), and from milk processing plants (148) (Table 2). *S. maltophilia* is able to survive in beverages (151). UV treatment has been recommended for use in hydroponic farms to reduce *S. maltophilia* biofilm on leafy green vegetables (154). These studies emphasize the need to improve sanitation and monitor these products for the presence of this multiple-drug-resistant pathogen. As an opportunist, the presence of this organism may pose a significant threat to susceptible patient populations.

In addition to its recognition as a human opportunist, *S. maltophilia* is emerging as an opportunistic veterinary pathogen of significance. *S. maltophilia* has been detected in mammals (179–185), birds (186, 187), fish (188–191), reptiles (192–195), insects (115, 196–205), marine invertebrates (206, 207), nematodes (208–211), and protozoa (212–216) (Table 5). *S. maltophilia* was denoted as a commensal, pathogen, or endocytobiont based on its recovery from a healthy or an infected animal (Table 5); it is clear from these studies that *S. maltophilia* can be a pathogen of certain species of mammals, fish, reptiles, insects, nematodes, and protozoa. A recent report proposed the moth fly as a mechanical vector for *S. maltophilia* disease (196). A recent molecular study of *S. maltophilia* strains from animals found some phylogenetic traits shared with human *S. maltophilia* strains (183). However, larger-scale studies are required to establish whether animals are a significant reservoir for *S. maltophilia* that causes infection in humans.

As *S. maltophilia* is a common water contaminant, it is important to understand its interaction with other waterborne microbes and humans. Amoebae (e.g., *Acanthamoebae*) have been reported to harbor *S. maltophilia* and may provide a reservoir host and mode of transmission of *S. maltophilia* to humans (212, 213, 215–217). *S. maltophilia* associated with amoebae has been recovered from hospital water samples (216, 217). *S. maltophilia* associated with amoebae in soil (214) is able to reside and replicate within the amoebae (215). Taken together, these observations are significant for public health. Infection by this opportunistic bacterial pathogen may also be community acquired (1, 53, 105, 218), and this poses a serious threat to immunocompromised individuals.

TABLE 4 Sources of *S. maltophilia*

Source	Reference(s)
Hospital	
Invasive devices	124
Water	138, 139
Positive expiratory pressure therapy device	135
Peritoneal dialysis catheter	126
Hemodialyzer	127
Intravascular catheter	128
Air	146
Hydrotherapy equipment	140
Flexible endoscopes	136, 137
Ventilator systems	141
Heater-cooler units	142
Hospital kitchen ICU tubing	143
Community	
Milk processing plant	148
Raw cow's milk	152
Ready-to-eat street foods	155
Cheese	149, 157, 158
Poultry meat	159
Edible ice	151, 156
Fresh vegetables	147, 150, 153, 154
Drinking water distribution systems	164–169, 171, 172
Dishwasher seal	160
Contact lens storage case	145
Dental biofilms	144
Groundwater	173
Seawater	161
River water	174
Wastewater	163, 170
Soil	176–178
Manure	175

New Methods of Detection

The continued increase in antibiotic resistance of *S. maltophilia* worldwide emphasizes the importance of early detection of this pathogen in infection. We have seen advances in cultivation and differential testing strategies. A new selective Steno medium agar (SMA) for *S. maltophilia* has been used to isolate the pathogen from sputum (219). The ease of preparation and recovery of *S. maltophilia* suggests that it could be useful to detect its presence within polymicrobial samples. The chromogenic β-LACTA test (BLT) has been assessed for detection of extended-spectrum β-lactamase (ESBL)-Gram-negative bacteria directly on bronchial aspirates (220). More research is needed to determine if the BLT can be applied to other types of clinical samples, e.g., blood or nervous system samples. The presence of specific DNase activity enables the differentiation between *S. maltophilia* and other nonfermenting Gram-negative bacteria (221). A modified DNase tube test for identification of *S. maltophilia* has shown positive results for various clinical samples (tracheal aspirate, pus, and urine) (222). These methods allow for putative qualitative identification of *S. maltophilia*. More rigorous testing is needed to confirm the identification of this pathogen.

Nucleic acid detection methods have been developed to detect pathogens in mixed-culture infections (105, 157, 223–231). These methods are limited as they do not differentiate between live and dead cells, but they can provide the clinical laboratory with results relatively quickly, resulting in appropriate treatment of infection without having to wait for culture growth and identification by conventional biochemical assays. Molecular typing methods for *S. maltophilia* have been reviewed recently; this review provides a list of advantages and limitations of these methods (232).

TABLE 5 *S. maltophilia* in animals

Animal	Hypothetical role of *S. maltophilia*	Reference(s)
Mammals		
Cat	Pathogen	181, 183
Dog	Pathogen	180
	Commensal	183
Pig	Pathogen	182
Horse	Pathogen	183, 185
Cow	Pathogen	179, 184
Birds		
California condor	Commensal	186, 187
Fish		
Catfish	Pathogen	188, 191
Frozen Antarctic krill	Food spoilage	190
Rainbow trout	Commensal	189
Reptiles and amphibians		
Frog	Pathogen	195
Prairie rattlesnake	Commensal	193
Salamander	Pathogen	194
Tortoise	Commensal	192
Insects and arachnids		
Asiatic rhinoceros beetle	Commensal	202
Cockroach	Commensal	201
Mosquito	Commensal	115, 205
Moth fly	Commensal	196
Bark beetle	Commensal	200
	Pathogen	204
Silkworm	Commensal	197
Spider	Commensal	203
Stable fly	Commensal	199
Vespine wasp	Commensal	198
Marine invertebrates		
Anemonia sulcata	Commensal	206, 207
Actinia equina		
Holothuria tubulosa		
Holothuria forskali		
Nematodes		
Mesorhabditis	Commensal	209
Caenorhabditis remanei	Pathogen	208
Pine wood nematode	Commensal	210, 211
Protozoa		
Acanthamoeba spp.	Pathogen	213
	Endocytobiont	215
Micriamoeba	Endocytobiont	214
Naegleria pringsheimi	Pathogen	213
Tetramitus	Endocytobiont	214
Vermamoeba vermiformis	Pathogen	212
	Pathogen	213
	Endosymbiont	216
Willaertia magna	Endocytobiont	215

PCR amplification of 16S rRNA genes has been used to detect *S. maltophilia* in human serum samples, and real-time PCR has quantified *S. maltophilia* flagellin gene copy numbers in peripheral blood leukocytes (223). A SeptiFast (SF) real-time PCR test has been used to identify *S. maltophilia* in bloodstream cultures from CF patients with febrile pulmonary exacerbation (224). PCR has been used to detect the *smeT* gene (encoding a transcriptional regulator of the SmeDEF multiple-drug efflux pump) of

S. maltophilia in cheeses (157). Quantitative real-time PCR using a conserved 4-kb genomic sequence has been used to identify *S. maltophilia* in sputum, blood, endotracheal tube, and other clinical samples (225). Multiplex PCR strategies have detected *S. maltophilia* in CF patient respiratory samples and in water samples with high background contamination (226, 227). Probes used in these methods should be tested to ensure they do not demonstrate any cross-reactivity between them and other nontarget species/strains. A loop-mediated isothermal amplification (LAMP) assay for rapid detection of *S. maltophilia* in respiratory samples of patients with pneumonia has demonstrated no cross-reactivity with other tested bacteria and, notably, no interference with amplification when the bacteria were mixed with organic compounds (228). The quick delivery of results and its sensitivity make the LAMP assay an attractive method for use in the clinical microbiology laboratory.

Diagnostic DNA microarrays and peptide nucleic acid fluorescence *in situ* hybridization (PNA FISH) allowed detection of *S. maltophilia* in intracranial bacterial/fungal infections and tracheal aspirate and bronchoalveolar lavage samples (229, 230). Application of the PNA FISH assay may be useful for studying the pathogen in its biofilm within chronically colonized patients. Other applications of these methods need to be explored using more clinical samples containing this pathogen.

Metagenomic sequencing has been used to identify *S. maltophilia* in spinal cord aspirate and blood samples from pediatric patients, enabling subsequent successful antimicrobial therapy and positive outcomes (35, 105). Direct-from-blood RNA sequencing has identified *S. maltophilia* in whole-blood samples from an immunocompromised patient with CF and lung transplant (231). These sequencing methods do not provide information about the organism's activity in the host. Next-generation sequencing (NGS) of microbial cell-free DNA (cfDNA) in plasma from chemotherapy or transplant patients with febrile neutropenia, sepsis, or infection has identified *S. maltophilia* (233), but larger studies are needed to validate the use of microbial cfDNA NGS for diagnostic applications.

Recent protein-based methods developed to observe *S. maltophilia* infection in patients have included a quantitative immunofluorescence assay that monitors the level of *S. maltophilia* colonization in CF patients (234) and a method that uses unique peptide markers and liquid chromatography-tandem mass spectrometry (LC-MS/MS) to detect *S. maltophilia* directly in bronchoalveolar lavage samples (235). It should be noted that to avoid cross-reactivity in the immunofluorescence assay, absorption with other pathogens may need to be performed prior to quantification of the antibody response to *S. maltophilia*. The LC-MS/MS methodology relies on the abundance of the selected peptide in each strain, and this limitation should be recognized if this method is to be used for clinical diagnosis of infection.

Volatile metabolites released by *S. maltophilia* may serve as useful biomarkers to distinguish this pathogen from other organisms found in lung infections (236–239). This noninvasive technique is attractive for use with patients. It should be noted that the volatile organic compound (VOC) profile patterns are influenced by stage of culture growth, being more readily distinguishable between bacterial species during logarithmic growth than during stationary growth (238). Fatty acid methyl esters (FAME) fingerprinting combined with a random amplification polymorphic DNA (RAPD) method provides a low-cost, high-throughput automated approach that may be useful for differentiation of bacterial species and phylogenetic analyses (239). Due to the relatively low number of samples used in these studies of volatile organic compounds, additional clinical and environmental *S. maltophilia* strains need to be tested to see whether there are clear differences in the production of these volatile metabolites. It remains to be determined how useful this approach is with CF patients and patients with lung infections.

Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) has been used to identify patient isolates of *S. maltophilia* (78, 240) and to identify bacterial pathogens in groundwater (173). For identification of clinical *S. maltophilia*, MALDI-TOF MS has demonstrated a high concordance rate with 16S rRNA gene sequencing

and superiority over conventional phenotypic identification (241). This method can be used to identify bacteria in urine and blood cultures but, in the case of blood, may require the removal of nonbacterial proteins prior to analysis (242). In a study, however, no identification of two *S. maltophilia* strains was possible with samples prepared using the MALDI Sepsityper kit (Bruker Daltonics, Billerica, MA) (243). The limitations of this kit were also seen in an earlier study where only 1 of 5 *S. maltophilia* strains was identified to the genus and species levels in comparison to that with standard phenotypic methods (244).

For more commonly encountered Gram-negative bacteria, the accuracy of MALDI-TOF MS for microbial culture identification is comparable if not superior to automated phenotypic culture identification systems (245). The updating of databases used with the MALDI-TOF MS system is important to ensure the accuracy of the method (242). MALDI-TOF MS may also be used to detect antibiotic resistance in bacterial pathogens (242, 245). Clinical laboratories are currently using MALDI-TOF MS in conjunction with automated identification systems and obtaining close to 100% correct identification (245).

A recent study using *S. maltophilia* ATCC 13637 and *Escherichia coli* ATCC 25922 reported the combination of collision experiments and redox activity of bacteria to identify single bacterial cells (246). *S. maltophilia* cell behavior contrasted with that of *E. coli* cells. Additional studies are needed to assess this approach using a variety of different bacterial species to see whether this combination approach can truly distinguish between the behaviors of the bacteria in single culture, polymicrobial cultures, and biofilms.

A summary of the methods described above, including their application, sensitivity, and accuracy, is presented in Table 6.

Genetics and Genomes of *S. maltophilia*

S. maltophilia demonstrates considerable genotypic and phenotypic diversity. Genome sequences of several *S. maltophilia* clinical and environmental strains have been recently reported (175, 247–250). The genomes of two type strains of *S. maltophilia*, ATCC 13637^T (175) and MTCC 434^T (250), have been published recently. The genomes of *S. maltophilia* clinical strains K279a (251) and D457 (252) have been published. Novel genomospecies have been identified for clinical *S. maltophilia* isolates (253).

Genomic comparisons between *S. maltophilia* K279a and two biocontrol agents, *S. maltophilia* R551-3 and *Stenotrophomonas rhizophila* DSM14405^T have shown that the genomes share significant sequence similarity (254). Strain-specific genes between *S. maltophilia* K279a and *S. rhizophila* DSM14405^T may be expressed in response to adaptation to their particular habitats.

Various methods, including repetitive extragenic palindromic-PCR (Rep-PCR) fingerprinting (255, 256), gene sequencing (257, 258), genome sequencing (47, 253, 259–263), pulsed-field gel electrophoresis (PFGE) (65, 258, 264–266), and multilocus sequence typing (MLST) (256, 267–269), have been used to compare clinical and environmental *S. maltophilia* strains. Worldwide, regardless of their origin, *S. maltophilia* strains demonstrate high genetic heterogeneity, with an open pangenome and shared core genome (Table 7). Phylogenetic analyses of 375 nonduplicated *S. maltophilia* complex genomes (including 104 of animal origin, 226 of human, 30 of environmental, and 15 of unknown origin) identified at least 20 genogroups; MLST analysis has shown the majority of strains in genogroups 1, 3, 6, and C are of human origin, and most of the strains in genogroups 2-b and 5 are of animal origin (269). MLST assessment of clinical *S. maltophilia* strains across multiple French hospitals confirmed previous published reports of genogroups (232, 270, 271) and observed a predominance of genogroups 6 and 2 (267); another MLST study of clinical *S. maltophilia* strains from multiple institutions in the United States classed them in genogroups 6, 1, and C (268). Subculturing of isolates prior to genetic analyses need to be minimized to reduce the possibility of increased mutation rates that can affect genotypic profiling (272). Genome sequencing studies have identified recombination events that contribute to genetic diversity (253, 263) and have shown no evidence of independent

TABLE 6 Methods used for detection of *S. maltophilia*[a]

Method	Application	Sample type	Target	Sensitivity, accuracy	Reference(s)
Nucleic acid					
PCR	Identification of bacterial DNA in human serum	14 type 1 diabetic patients and 15 healthy non-diabetic control subjects	16S rRNA gene	Positive identification of *S. maltophilia*, NA	223
	Identification of *S. maltophilia* in cheeses	31 microbial DNA samples from fresh cheeses	*smeT* gene	22 matches with *S. maltophilia*, NA	157
Quantitative real-time PCR	Identification of *S. maltophilia*	88 patient *S. maltophilia* isolates and *S. maltophilia* control LMG 957	Conserved 4-kb genomic sequence	LOD of ∼5 fg/μl or ∼9 GEs, 100%	225
Multiplex real-time PCR	Diagnostics assay using probe to *ssrA* gene to detect *S. maltophilia*	10 *Stenotrophomonas* species/strains	*ssrA* gene	LOD of 9.5 GEs, no cross-reactivity between nontarget species or strains	227
Multiplex PCR	Detection of *S. maltophilia* in CF patient respiratory samples	34 *S. maltophilia* isolates from CF respiratory samples	*metB* gene	LOD of 10^3 CFU/ml, 85%	226
LAMP	Detection of *S. maltophilia* directly from patient respiratory samples	Samples from BAL, endotracheal aspirate, and BAS	Primers based on *stmPr* gene	LOD of 10^4 CFU/ml, no cross-reactivity with other tested bacteria. Accuracy between LAMP and culture of 88% for BAL samples, 95% for BAS/EA samples	228[b]
DNA microarray	Detection *S. maltophilia* in intracranial infections	88 cerebrospinal fluid samples	16S rRNA gene	LOD of 10 CFU/ml, no cross-reactivity of probe with other microorganisms	229
Metagenomic sequencing	Identification of *S. maltophilia* in spinal cord aspirate, blood	Patient with *S. maltophilia* discitis, patient with severe pneumonia	NA	Positive identification of *S. maltophilia*	35, 105
Direct-from-blood RNA sequencing	Identification of *S. maltophilia* in whole blood	Immunocompromised CF patient with lung transplant	NA	Positive identification of *S. maltophilia*	231
Next-generation sequencing of microbial cell-free DNA	Identification of microbial cell-free DNA in plasma of chemotherapy or transplant patients	10 patient blood samples	NA	70% agreement with conventional diagnostic lab protocols	233
Peptide nucleic acid fluorescence *in situ* hybridization	Detection in tracheal aspirates and bronchoalveolar lavage	35 clinical human and veterinary *S. maltophilia* isolates	16S rRNA	LOD of 10^4 CFU/ml, 100%	230
Protein					
DNase test	Distinguish *S. maltophilia* from other nonfermenting Gram-negative bacteria	64 *S. maltophilia* patient isolates	DNase activity	100% positive identification at 12 h incubation	222
β-Lactamase (chromogenic β-LACTA test)	Identification of ESBL-Gram-negative bacteria directly in bronchial aspirates	76 patient bronchial aspirates with ≥10^4 CFU/ml	β-Lactamase activity	Identification of 7 *S. maltophilia*, 5 of which were 5 ESBL-producers	220
Immunofluorescence assay	Quantitative detection of *S. maltophilia* antibodies in CF patient sera	64 CF patient and 36 healthy subject serum samples	*S. maltophilia*	No cross-reactivity with *P. aeruginosa*, antibody levels higher in CF chronically colonized with *S. maltophilia* (sensitivity of 70.7% and specificity of 84.7%)	234

(Continued on next page)

TABLE 6 (Continued)

Method	Application	Sample type	Target	Sensitivity, accuracy	Reference(s)
LC-MS/MS	Identification of *S. maltophilia* directly from bronchoalveolar lavage samples	7 BAL samples from healthy subjects spiked with *S. maltophilia* ATCC 51331	Strain-specific peptide-markers	LOD of 10^4 CFU, NA	235[b]
Volatile compounds					
SPME/GC-MS	Identification of biomarkers for *S. maltophilia*	15 clinical and 5 environmental *S. maltophilia* strains	Dimethyl trisulfide, 3-methyl-1-butanol, 2-methyl-1-butanol	100%, NA	236
SIFT-MS	Identification of compounds produced specifically by *S. maltophilia*	10 *S. maltophilia* patient isolates	Aldehydes (butanol, pentanol, propanal, hexanal)	Volatile compound concn is culture medium dependent, NA	237
GC×GC-TOFMS	Differentiation of *S. maltophilia* from other CF-associated bacteria	1 *S. maltophilia* strain	VOC pattern	Growth phase and culture storage affected production of VOCs, no differentiation of *S. maltophilia* from other CF-associated bacteria	238[b]
GC-MS	Typing of *S. maltophilia* clinical isolates	35 *S. maltophilia* patient isolates	Fatty acid methyl ester profile	Concordance rate with RAPD typing of 69%	239
Bioanalytes					
MALDI-TOF MS	Identification of spectral pattern of bioanalytes for *S. maltophilia*	50 *S. maltophilia* patient isolates	Ion molecules	100% identified at genus level and 50% identified at species level, no isolates were misidentified	240
	Identification of *S. maltophilia* in outbreak of acute endophthalmitis	28 vitreous patient samples	Ion molecules	All samples were positive for *S. maltophilia* and confirmed by DNA sequencing	78
	Identification of *S. maltophilia* in groundwater	Groundwater samples from 7 wells	Ion molecules	Two samples contained *S. maltophilia* and identification was confirmed by 16S rRNA sequencing	173
Cell behavior					
Collision and redox activity measurements	Identification of single cells of *S. maltophilia*	*S. maltophilia* ATCC 13637	Oxidation/reduction activity of a cell	Charge-transfer events during collisions in *S. maltophilia* differs from those of *E. coli* ATCC 25922, NA	246

[a]LOD, limit of detection; NA, not available; GEs, genome equivalents; CF, cystic fibrosis; LAMP, loop-mediated isothermal amplification; BAL, bronchoalveolar lavage; BAS, bronchoaspirate; EA, endotracheal aspirate; ESBL, extended-spectrum β-lactamase producing; LC-MS/MS, liquid chromatography-tandem mass spectrometry; SPME/GC-MS, solid-phase microextraction gas chromatography-mass spectrometry; SIFT-MS, selected ion flow tube mass spectrometry; GC×GC-TOFMS, two-dimensional gas chromatography–time of flight mass spectrometry; VOC, volatile organic compound; GC-MS, gas chromatography-mass spectrometry; RAPD, random amplification polymorphic DNA; MALDI-TOF MS, matrix-assisted laser desorption ionization–time of flight mass spectrometry.

[b]Proof of concept study.

TABLE 7 Genetic analyses of *S. maltophilia*

Method(s)	*S. maltophilia*	Main observations	Reference
Rep-PCR fingerprinting and partial *gyrB* sequencing	Environmental, clinical, Germany, Ireland, USA, Sweden	Presence of potential virulence genes in all isolates	255
PCR, DNA sequencing, DNA-DNA hybridization, *in silico* comparisons of *gyrB* gene	Environmental, clinical, Culture Collection University of Gothenburg, Sweden	Strains shared 93–99% sequence similarity of *gyrB* gene	257
Rep-PCR and MLST	Clinical, hospitals in Iran	High genetic diversity	256
MLST	Clinical strains, multiple hospitals and centers, mostly from France	Predominance of genogroups 6 and 2	266
	Strains from U.S. hospitals, universities, and centers	Predominance of genogroups 6, 1, and C for clinical strains	267
	Animal, human, environmental, unknown origin, mostly from France	Open pangenome of 22,936 genes, core genome of 1,740 genes. High genetic diversity with most human strains in genogroups 1, 3, 6 and C, most animal strains in genogroups 2-b and 5	268
16S rRNA gene sequencing, MLST, PFGE	Clinical strains from non-CF and CF patients, hospital in Serbia	High genetic diversity across strains and phenotypic differences between non-CF and CF strains	258
PFGE	Clinical, hospitals in Mexico	Multiple distinct PFGE types	266
	Environmental, clinical, hospital in Thailand	High genetic diversity, no genotypic relationship found between environmental and clinical strains	264
	Clinical from hospitals in Italy, environmental from Czech Republic	High genetic heterogeneity with no difference between CF and non-CF strains	265
	Clinical, from lungs of chronically infected CF patient across a 10-yr period	Growth rate of strains increased over time with a decrease in biofilm formation, virulence, and antibiotic susceptibility	65
Genome sequencing-based phylogenomic core single nucleotide polymorphism	Clinical, environmental from multiple institutions in Germany	High genomic diversity	259
Genome sequencing	Clinical, hospital in India	Shared core-genome, homologous recombination and nonhomologous gene transfer contributed to genetic diversity	253
	Biopsy sites of a set of explanted CF lungs	Adaptive evolution and positive selection of genes	47
	Clinical, CF pediatric patients in Italy over a 12-yr period	High genomic heterogeneity with a weak genotype-phenotype correlation	260
	Clinical from hospitals in Spain and the UK, environmental from Netherlands, Germany, USA, and Brazil	Strains showed no distinct independent evolutionary lineages	261
Genome sequencing and genomic analysis comparison to published strains	Clinical from Australia, Spain, UK, and China, environmental from Burkina Faso, France, Brazil, UK, USA, China, Norway, and Portugal	No significant relationship between strain's source, clade assignment, or antibiotic susceptibility	262
Bioinformatics and analyses of genome sequences	Clinical from China, USA, Netherlands, and Germany, environmental from USA, Philippines, UK, Netherlands, China	Shared large open pan-genome and shared core genome of 887 genes, recombination events contributed to genetic heterogeneity	263

evolutionary lineages (261) (Table 7). A recent study has reported strains of *S. maltophilia* lineages that are associated with human infections and clinical settings and propose lineage Sm6 to be most suitable for infecting humans (273). These genomic studies underscore the challenge of trying to dissect out the differences between clinical and environmental *S. maltophilia*.

As *S. maltophilia* is seen often in CF patients, particular attention has been focused on comparing non-CF *S. maltophilia* strains with CF strains. While genetic heterogeneity is observed, studies have not shown strong genotype-phenotype correlation among these strains (Table 7). Both global and local selection pressure forces are evident for *S. maltophilia* in the CF lung. Phylogenetic analyses of 552 isolates recovered from 23 biopsy sites of a set of explanted CF lungs revealed multiple coexisting

lineages, with major lineages present across most of the lung sites and the dispersal of new mutations out of a lung site (47). PFGE analyses of *S. maltophilia* strains recovered from the lungs of a chronically infected CF patient across a 10-year period categorized the 13 strains into two groups and two different pulsotypes within each group; growth rates of the strains significantly differed and increased over time, with a decrease in biofilm formation, virulence, and antibiotic susceptibility (65) (Table 7). It is apparent that *S. maltophilia* strains adapt according to their external niche. For example, exposure to acidic pH impairs the growth of CF and non-CF strains (274). In another example, altered transcripts for those used in metabolism, stress response, and drug resistance were observed in CF strains exposed to synthetic CF sputum medium (275). It is evident from these studies that *S. maltophilia* adapts to the human CF lung niche. Further work is needed with models of infection to establish other factors that act as selection pressures on strains colonizing different areas of the host lung.

Manipulating *S. maltophilia* genetics. Research into the molecular mechanisms used by *S. maltophilia* has required the development of suitable genetic engineering tools. Protocols for genomic DNA isolation, extraction of DNA for use with PCR, RNA extraction, transfer of plasmid DNA into *S. maltophilia*, and the use of pEX18TC to generate allelic exchange mutants have been described for *S. maltophilia* K279a and may be optimized for use with other strains (276).

An arabinose-inducible system in *S. maltophilia* has been developed (277). The arabinose inducible expression vector, pBBad22T, contains the pBBR1MCS-4 replicon, a mobilization (mob) element that permits plasmid transfer by conjugation, multiple cloning restriction enzyme sites, the P_{BAD} promoter and *araC* (codes for repressor protein), and a tetracycline resistance marker. Plasmid pBxylE is an *araC*-P_{BAD}::*xylE* recombinant plasmid that can be introduced into *S. maltophilia* by conjugation and used to assess inducibility of pBBad22T (277). The expression vector pBBad22T can be useful for the cloning, expression, and future targeted mutation of genes in *S. maltophilia*.

High-efficiency transformation of environmental *S. maltophilia* S21 by electroporation with plasmid pBBR1MCS has been reported (278). Electroporation of *S. maltophilia* using the EZ:: TN<R6K1ori/KAN-2>Tnp transposome mutagenesis kit (Epicenter Technologies, WI) has been successfully achieved and generated transposon mutants that were used to identify genes important for biofilm formation, lipopolysaccharide synthesis, and assembly (279, 280).

MOLECULAR MECHANISMS OF PATHOGENESIS

S. maltophilia is considered to be an opportunistic pathogen of low virulence that is multidrug resistant and produces various extracellular enzymes, including DNase, proteases, lipases, hyaluronidase, and hemolysin. *S. maltophilia* is associated with a decrease in lung function and forms biofilms in infected patients that are challenging for the physician to treat. In each subsection below, this review focuses on presenting the reader with some background information for context and emphasizes updated information (since the author's last review in 2012) (1) about the mechanisms used by *S. maltophilia* during pathogenesis. Figure 1 illustrates properties of *S. maltophilia*; for clarity of viewing, not all properties are shown. A summary of pathogenic mechanisms is presented in Table 8.

Various models have been used to study *S. maltophilia in vivo*. Mice (281, 282), rats (283), *Caenorhabditis elegans* (284), zebrafish (285), and *Galleria mellonella* (wax moth) (286) have been used to study *S. maltophilia* pathogenesis and infection. These models have provided a better understanding of the host-pathogen interactions. BALB/c mice treated with *S. maltophilia* fimbrin demonstrate a specific host immune response (IL-1β, TNF-α, and increased phagocytic activity) (281). The role of YajQ as a cyclic di-GMP effector was clarified as contributing to the adherence, colonization, and persistence of *S. maltophilia* in the murine (C57BL/6 mice) host (282). The effects of moxifloxacin on host lipid peroxidation and inflammation have been examined in immunosuppressed Wistar rats treated with this antimicrobial against *S. maltophilia* soft tissue infection (283). A study

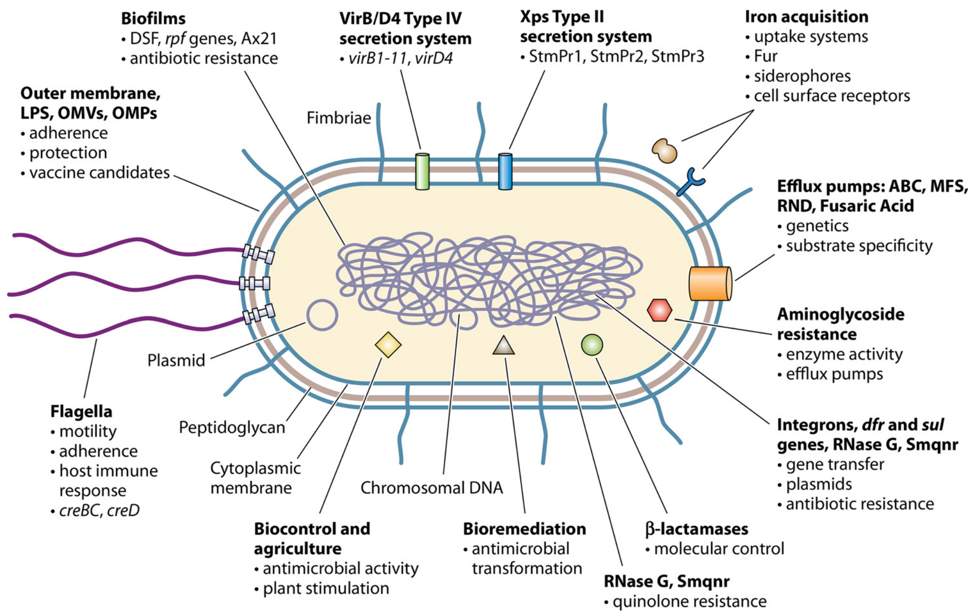

FIG 1 Properties of *S. maltophilia*. For clarity of viewing, not all properties are shown. Not drawn to scale.

using *C. elegans* and *S. maltophilia* clinical invasive isolates has established that direct contact is not required for *S. maltophilia* to kill its host (284). The zebrafish model of infection and differential proteomic analyses have identified the expression of the Ax21 quorum-sensing factor as correlating strongly with host mortality, adherence to HeLa cells, and serum sensitivity (285). *G. mellonella* larvae have been used to identify the role of Hfq (host factor I protein), an RNA chaperone, in the virulence of *S. maltophilia* K279a (286). Virulence of a deletion mutant (Δ*hfq*) was comparable to that of K279a against *G. mellonella* larvae, while the mutant demonstrated impaired motility, biofilm formation, adherence to and invasion of IB3-1 bronchial epithelial cells, and ability to replicate in RAW 264.7 murine macrophages. In summary, use of these animal models has enabled us to identify general and specific changes that occur in the host during *S. maltophilia* infection. Drug therapy development strategies benefit from these studies in which host-pathogen interactions are considered and possible suitable targets for anti-infection strategies are identified.

S. maltophilia produces an array of enzymes that serve as virulence factors and help protect this pathogen against host defenses. Gelatinase, hemolysin, hyaluronidase, lipase, proteinase, and DNase have been identified in *S. maltophilia* (287). A putative alginate lyase has been identified in *S. maltophilia* K279a and found to have a pH-mediated substrate specificity for alginate, poly-β-D-glucuronic acid, and hyaluronic acid (288). Further characterization is needed to identify a possible role for this alginate

TABLE 8 Pathogenic mechanisms of *S. maltophilia*

Role	Structure(s)[a]
Antimicrobial resistance	Efflux drug pumps, class I integrons, reduced outer membrane permeability, antimicrobial modifying or degrading enzymes, OMVs
Motility	Flagella, type IV pili
Adherence to surfaces	Flagella, fimbriae, LPS
Damage to host	Protein secretion systems, extracellular enzymes, including proteinases, lipase, DNase, gelatinase, lecithinase, heparinase, hemolysin, and hyaluronidase
Acquisition of iron	Siderophores, siderophore and heme-mediated iron uptake systems
Biofilms	Diffusible signal factor and quorum sensing system
Protection of pathogen against host defenses	Superoxide dismutases, melanin, catalase, and hydroperoxidase

[a]OMVs, outer membrane vesicles; LPS, lipopolysaccharide.

lyase in the pathogenesis of *S. maltophilia* and/or during interaction with other microorganisms. Protection of *S. maltophilia* against damage by the host defenses is provided by the production of a manganese-dependent superoxide dismutase (MnSOD; SodA) and an iron-dependent SOD (FeSOD; SodB) (289), catalase (Kat), an alkyl hydroperoxidase (Ahp) (290), and the pigment melanin (287). It is clear from these studies that *S. maltophilia* has a substantial arsenal to infiltrate and damage the susceptible host while protecting itself.

Antimicrobial Resistance

S. maltophilia is intrinsically resistant to a wide range of antibiotics, including β-lactams, carbapenems, fluoroquinolones, tetracyclines, chloramphenicol, aminoglycosides, polymyxins, macrolides, and TMP-SMX (1). As part of its multiple-drug resistance, *S. maltophilia* has been reported to use plasmid-mediated antimicrobial resistance, integrons, and insertion sequence common region (ISCR) elements, SmQnr determinants, modification of antibiotics, and efflux pumps (1).

TMP-SMX continues to be a drug of choice for treatment of *S. maltophilia*, though reports of resistance have emerged (4, 268, 291). During 2009 to 2012, results from the SENTRY antimicrobial surveillance program of pneumonia patients in U.S. and European hospitals showed that 96.3% of 302 *S. maltophilia* isolates were susceptible to TMP-SMX (4). In a recent study of isolates recovered from U.S. centers during 2006 to 2016, the susceptibility of 130 *S. maltophilia* isolates to TMP-SMX ranged from 79% to 96% (268). These studies underscore the importance of continuing to monitor this rise in resistance while developing new antimicrobials against this human opportunist.

Laboratory experimental evolutionary studies have been geared toward a deeper understanding of the molecular mechanisms of antimicrobial resistance at play in *S. maltophilia* (292–295). Some interesting findings have emerged from these studies that should be considered when administering antibiotics to treat *S. maltophilia* infections. A study demonstrated that the alteration of the intrinsic resistance in *S. maltophilia* affects the mutant selection window and suggested that inhibition of this intrinsic resistance could result in selection of *S. maltophilia* antibiotic-resistant mutants at low antibiotic concentrations (295). Resistance to a particular antibiotic may be provided to *S. maltophilia* through its use of different efflux pumps. The ability of *S. maltophilia* to acquire quinolone resistance appears linked with its intrinsic resistome, with the type of quinolone resistance mediated by which efflux pumps are functional and the degree to which they are expressed (294).

Recent studies have shown that exposure of *S. maltophilia* to increasing concentrations of an antimicrobial can result in genomic changes without cost of bacterial fitness (292) or in genomic mutations that are associated with a fitness cost (293). Increasing concentrations of ceftazidime, for example, resulted in mutation of the resistance-nodulation-division (RND) efflux pump transporter *smeH*, which ultimately led to resistance to other β-lactam drugs (292). These studies clearly demonstrate that exposure to antimicrobials can trigger changes in efflux pumps and unleash new mechanisms of antimicrobial protection for *S. maltophilia*.

In addition to efflux pumps that expel antimicrobials out of the bacterial cell, proteins involved in uptake of antimicrobials can provide a mechanism for resistance. The TonB energy transducer in *S. maltophilia* mediates uptake of ceftazidime, and clinical *S. maltophilia* isolates with TonB mutations exhibit resistance to siderophore-conjugated lactivicin (296). This is an important observation as it raises the concern that emergence of *S. maltophilia* strains with mutations in TonB may limit the use of recently developed siderophore-conjugated antimicrobials.

In the subsections below that describe mechanisms of antimicrobial resistance, research advances since the last review by the author are the focus of interest. Background information about the general mechanisms of antimicrobial resistance used by *S. maltophilia* can be found in the previous review (1).

β-Lactam resistance. There are complex and compensatory mechanisms used by *S. maltophilia* for the expression and activity of its two chromosomally encoded

β-lactamases, L1 and L2. NagZ (a β-*N*-acetylglucosaminidase)-dependent and NagZ-independent mechanisms are important for β-lactamase expression (297). *S. maltophilia* harbors the *mrcA* gene (encodes penicillin-binding protein 1α) and regulatory proteins AmpR (transcriptional regulator) and AmpN-AmpG (permease system) that influence basal β-lactamase activity (298). Inactivation of *mltD1* (encodes lytic transglycosylase D1) results in increased uninduced β-lactamase activity and upregulated expression of L1 and L2 β-lactamase genes (299). The function of AmpN/AmpG permease and AmpR is essential to the *mltD1* mutant phenotype, and disruption of *nagZ* results in partial decrease of the uninduced β-lactamase activity. Disruption of *mltD1* also leads to *creBC*- (codes for a two-component regulatory system) and *ampNG*-dependent increased expression of *mltB1* and *mltD2* (code for two other lytic transglycosylases) (299). Disruption of the *mrcA* gene, $ampD_1$ gene (codes for enzyme used in peptidoglycan recycling), and at least one other gene results in the hyperproduction of β-lactamase by *S. maltophilia* (300).

The exposure of a bacterium to an antimicrobial agent can lead to altered protein expression and subsequent antimicrobial resistance. For example, exposure of *S. maltophilia* clinical isolate 44/98 (LM 26824) to imipenem (25 μg/ml) increased β-lactamase production and expression of select proteins (for several efflux pumps, membrane transport, peptidoglycan biosynthesis, flagellin, ATP-dependent ClpX and ClpA, UvrB, the two-component system response regulator GGDEF signaling protein, protein translation, and metabolism) (301).

Aminoglycoside resistance. *S. maltophilia* has demonstrated resistance to aminoglycosides through different enzyme activities and efflux pumps (302). A new aminoglycoside modifying enzyme, 6′-*N*-aminoglycoside acetyltransferase [AAC(6′)-Iak], has been identified in *S. maltophilia* that contributes to reduced sensitivity to aminoglycosides (303). Two proteases, ClpA and HtpX, have been shown to contribute to the intrinsic aminoglycoside resistance of *S. maltophilia* (304).

Quinolone resistance. RNase G inactivation, important for mRNA stability and gene expression regulation (305), has been shown to decrease susceptibility of *S. maltophilia* to quinolones (306). Overexpression of the heat shock response genes has also been observed when RNase G is inactivated. Efflux pumps also contribute to quinolone resistance in *S. maltophilia*, and these pumps are discussed below.

Class I integrons and *dfrA* and *sul* genes. Class 1 integrons have been found to contribute resistance to kanamycin, tobramycin, and TMP-SMX in *S. maltophilia* clinical isolates (307). A class 1 integron was found in *S. maltophilia* that harbored a *sul1* gene and an *aadA2* gene (encodes aminoglycoside resistance) within the resistance gene cassette (308). The class 1 integrons provide a mechanism for the dissemination of antimicrobial resistance genes among *S. maltophilia* strains. *S. maltophilia* has acquired *sul* and *dfrA* genes in a plasmid-mediated class I integron, resulting in resistance to TMP-SMX (309). There is potential for horizontal gene transfer and the spread of resistance to TMP-SMX among *S. maltophilia* strains. The *sul1* gene has been observed linked to class 1 integrons in *S. maltophilia* exhibiting resistance to TMP-SMX (310). Horizontal gene transfer and recombination are both molecular mechanisms used by *S. maltophilia*.

Efflux pumps. *S. maltophilia* uses several efflux pumps that enable resistance to antimicrobials, including quinolones, aminoglycosides, beta-lactams, tetracyclines, erythromycin, and chloramphenicol. It is important to understand the molecular mechanisms needed for the pumps to function as they may be targets for pharmacological therapy.

(i) ABC family. The MacABCsm efflux pump of *S. maltophilia* has been shown to be important for drug resistance against aminoglycosides, macrolides, and polymyxins, biofilm formation, and protection against oxidative and envelope stresses (311). A two-component regulatory system of *macS* (sensor kinase MacS) and *macR* (response regulator MacR) is positioned upstream of the *macABCsm* operon. $TolC_{sm}$ is probably an outer membrane protein (OMP) that interacts with MacAB to generate a functional efflux pump. The *macABCsm* operon is conserved among *S. maltophilia* genomes (311). An earlier study examined the role of the *pcm-tolCsm* operon in drug resistance and

showed the operon to be highly conserved across several *S. maltophilia* genomes (312). $TolC_{sm}$ has been suggested to play a central role in drug resistance across several efflux pumps (311–314).

The ATP-binding cassette (ABC) efflux pump SmrA has been shown to confer increased resistance to fluoroquinolones and tetracycline (315). Checkerboard titration assays demonstrated synergistic activity between the combination of anti-SmrA antibody with antibiotics (e.g., ticarcillin-clavulanate, ciprofloxacin, and co-trimoxazole) seen in 33.3% of the tested *S. maltophilia* strains, while additive activity was observed for 38.1% of the strains, and indifferent activity was shown in 28.6% of the strains. Further work is needed to examine the precise mechanism of action of this polyclonal antibody. Research to identify antibodies that display broad substrate specificity across additional efflux pumps, may lead to the use of antibodies to increase the antimicrobial susceptibility of *S. maltophilia*.

(ii) MFS family. The major facilitator superfamily efflux pump of *S. maltophilia*, EmrCABsm, has been reported to extrude hydrophobic antimicrobials, including nalidixic acid, the oxidative phosphorylation uncoupler 3-chlorophenylhydrazone (CCCP), tetrachlorosalicylanilide (TCS), and erythromycin (316). Deletion of the EmrCABsm pump restored susceptibility to nalidixic acid, CCCP, TCS, and erythromycin. EmrRsm is a repressor of the *emrRCABsm* operon. Both *emrCsm* and *emrABsm* are needed for the EmrCABsm pump to function (316).

The major facilitator superfamily protein MfsA of *S. maltophilia* is an efflux pump that reduces susceptibility to aminoglycosides, cephalosporins, fluoroquinolones, rifampin, chloramphenicol, erythromycin, tetracycline, and paraquat (317, 318). SoxR is a transcriptional regulator that senses redox cycling drugs/superoxide and controls expression of *mfsA*; in its reduced form, SoxR represses *mfsA* expression, and in its oxidized form, SoxR activates *mfsA* expression (318). The *mfsA* gene has been found in the genomes of *S. maltophilia* strains D457, JV3, and R551-3, suggesting that it is common in this pathogen (317). Overexpression of MfsA on plasmid pMfsA was reported to increase resistance of *S. maltophilia* to fluoroquinolones and paraquat (319). The heterologous expression of *S. maltophilia mfsA* in *Agrobacterium tumefaciens*, *Burkholderia thailandensis*, *P. aeruginosa* PA14, and *E. coli* K-12 demonstrated that plasmid transfer of fluoroquinolone resistance and paraquat resistance from *S. maltophilia* to these microorganisms is possible (319).

(iii) RND family. The genome of *S. maltophilia* K279a shows eight RND-type efflux systems to be present: SmeABC, SmeDEF, SmeGH, SmeIJK, SmeMN, SmeOP, SmeVWX, and SmeYZ (251). Overexpression of the SmeABC efflux pump has been reported to contribute resistance to the quinolones ciprofloxacin and levofloxacin (320).

The SmeDEF efflux pump has been shown to contribute to resistance against quinolones, TMP-SMX, tetracycline, macrolides, and chloramphenicol (294, 295, 321–326). SmeT is a transcriptional regulator that represses expression of *smeDEF*; triclosan has been found to bind SmeT, resulting in induced expression of *smeDEF* and reduced susceptibility to ciprofloxacin (321). Flavonoids have been reported to be effectors of SmeT and induce *smeD* expression (322). The importance of a functional SmeDEF pump for bacterial colonization has been demonstrated (322). Antimicrobial testing of clinical *S. maltophilia* strain D457 and two isogenic mutants, D457R that overexpressed the efflux pump SmeDEF and MBS411 containing a deletion of the *smeE* gene, demonstrated that this efflux pump mediates resistance to TMP-SMX, trimethoprim, and sulfamethoxazole (323). Whole-genome sequencing of serial clinical isolates from a patient with *S. maltophilia* bacteremia revealed a single-nucleotide variant in *smeT* that inactivated the repressor function of SmeT and subsequently led to increased expression of *smeDEF* and multidrug resistance (324). This last observation is significant, as occurrence of this particular mutation in *smeT* appears likely within *S. maltophilia* strains harbored by patients. This possibility of such a scenario increases our awareness to monitor patients for signs of drug therapy failure and/or consider alternatives to using quinolones as a monotherapy.

Inactivation of *smeT* and consequent overexpression of the SmeDEF efflux pump has been shown to increase sensitivity of *S. maltophilia* to aminoglycosides; the observed aminoglycoside sensitivity was actually due to downregulation of *smeYZ* (325). This is an important observation as it suggests regulatory mechanisms connect these efflux pumps.

A SmeGH-TolCsm pump has been reported in *S. maltophilia* (313). The overexpression of SmeGH has been reported to contribute to the resistance of *S. maltophilia* to fluoroquinolones, macrolides, chloramphenicol, and tetracycline (313).

A type of coordinated overexpression of *smeJK* and *smeZ* has been identified in *S. maltophilia* that resulted in extended drug resistance, with increased MIC values for aminoglycosides, tetracyclines, and ciprofloxacin and resistance to levofloxacin (327). As mentioned above, this study too points to a regulated synchronized/integrated expression of these different RND efflux pumps.

The SmeIJK pump of *S. maltophilia* strain has been studied and antimicrobial susceptibility testing has suggested that the *smeJ* and *smeK* genes may be partially functionally redundant (328). The expression of the *smeIJK* operon is regulated by RpoE-mediated envelope stress response, and cell envelope integrity appears compromised if the operon is nonfunctional (328). Further work is needed to establish whether this pump provides protection against envelope stressors found within animal models of infection.

The SmeOP-TolC$_{sm}$ efflux pump of *S. maltophilia* contributes to multidrug resistance (314). SmeRo is a repressor of expression of *smeOP*. Antimicrobial susceptibility testing indicated that TolC$_{sm}$ may play a role in the activity of the SmeOP pump to extrude a variety of compounds, including antibiotics from different classes, and TolC$_{sm}$ may also contribute to efflux pumps in *S. maltophilia* (314). This observation again suggests that there is interplay at work between these efflux pumps.

The SmeVWX pump is a member of the RND family reported to provide *S. maltophilia* with resistance to aminoglycosides and contributes to multidrug resistance (329). The *smeU1-V-W-U2-X* operon is regulated by the *smeRv* gene. Overexpression of the SmeVWX pump contributes to resistance to chloramphenicol, quinolones, and tetracyclines (329). Vitamin K$_3$ has been identified as an inducer of the SmeVWX pump in *S. maltophilia* (330). Antibiotic disc and checkerboard assays confirmed that vitamin K$_3$ reduced susceptibility to chloramphenicol and ofloxacin. As plants produce vitamin K$_3$, this suggested that the SmeVWX pump is involved in plant-microbe interactions (330). This study highlights the idea that efflux pumps have multiple functions beyond shuttling of antimicrobials out of the bacterial cell.

Recently, the contributions of SmeDEF, SmeVWX, and SmQnr to fluoroquinolone resistance in *S. maltophilia* were examined (331). The SmeVWX pump was found to contribute more than the SmeDEF pump to fluoroquinolone resistance. Inactivation of Sm*qnr* increased susceptibility to fluoroquinolone, while overexpression of *smeDEF* did not contribute significantly to fluoroquinolone resistance (331).

The constitutively expressed SmeYZ efflux pump of *S. maltophilia* confers resistance to aminoglycosides and is likely important for oxidative stress alleviation (327, 332). TolC$_{sm}$ has been proposed as an OMP for SmeYZ (312). Further research is needed to determine the role played by this pump in mediating virulence of *S. maltophilia*. In addition to expression of efflux pumps as a defense against antimicrobials, it is important to remember that mutations in commonly used proteins can lead to altered antimicrobial sensitivity. For example, a mutation in the 50S ribosomal protein L1 (RplA) has been shown to activate production of efflux pump SmeYZ in *S. maltophilia* (333). This study raises our awareness of mutations that may occur in everyday proteins and lead to drug resistance.

In *S. maltophilia*, the regulation of expression of the SmeYZ and SmeDEF efflux pumps appears to be under the control of the SmeSyRy two-component regulatory system (334). Increased expression of the SmeDEF pump was shown to provide compensation for decreased expression of the SmeYZ pump. Interestingly, as transcription expression and promoter activity assays indicated that SmeRy does not play a role in

the increased expression of *smeDEF* or antibiotic susceptibility, the sensor, SmeSy, may interact with other response regulators (334). Future work is needed to more fully elucidate such interactions.

The PhoP protein (a DNA-binding response regulator of the PhoPQ two-component regulatory system) of *S. maltophilia* has been reported to regulate antimicrobial susceptibilities (335). Antimicrobial sensitivity testing of a *phoP* mutant showed increased sensitivity across a broad range of antimicrobials, including aminoglycosides, polymyxins, β-lactams, and chloramphenicol. PhoP has been shown to respond to low Mg^{2+} concentrations, regulate *smeZ* expression, and regulate genes involved in bacterial cell membrane permeability (335). In summary, the identification of the regulators of efflux pump expression and in-depth characterization of proteins such as $TolC_{sm}$, which is a major contributor to drug resistance, can help identify new pharmaceutical targets and strategies against *S. maltophilia*.

(iv) Fusaric acid efflux pump. A fusaric acid efflux pump, FuaABC, and its transcriptional regulator, FuaR, have been identified in *S. maltophilia* (336). The pump is induced by fusaric acid. Experiments using selected antibiotics of different classes established that the FuaABC pump only extrudes fusaric acid and that its function is dependent on a membrane proton gradient (336).

(v) Efflux pump inhibitors and inducers. Inhibition of its drug efflux pumps is a strategy that should diminish the drug resistance capability of a pathogen. Six efflux pump inhibitors [CCCP, phenyl-arginine-β-naphthylamide, 1-(1-naphthylmethyl)-piperazine, omeprazole, verapamil, and reserpine] have been assessed for their effect on colistin (COL) resistance in multidrug-resistant Gram-negative bacteria, including *S. maltophilia* (337). Compared with COL alone, COL with CCCP was the most effective combination, reducing the MIC range 1- to 4-fold (0.5 to 2 mg/liter versus 0.125 to 0.5 mg/liter) against COL-susceptible *S. maltophilia* and reducing the MIC range 64- to 1,024-fold (16 to 256 mg/liter versus 0.125 to 1 mg/liter) against COL-resistant *S. maltophilia*. Regrowth was observed among the COL-resistant *S. maltophilia* isolates at $>$24 h after challenge with COL and CCCP together (337). Studies such as this one enable us to increase the sensitivity of *S. maltophilia* to older drugs used in treatment as well as provide insight into new strategies for the development of specific inhibitors of particular efflux pumps.

A Biolog phenotype microarray has been developed with the goal of identifying multidrug resistance efflux pump inducers (338). This methodology used microtiter plates in combination with yellow fluorescent protein-based reporters of *S. maltophilia* efflux pumps SmeVWX and SmeYZ to screen for inducers. This approach should be tested using other efflux pumps. This combination strategy has the potential to uncover scenarios for the development of novel efflux pump inhibitors.

Biocide resistance. A study has determined that the risk of antibiotic resistance selection by biocides is likely low in *S. maltophilia* due to fitness cost (339). In this study, benzalkonium chloride bound SmeT and induced *smeD* expression in *S. maltophilia*. Examination of benzalkonium chloride-resistant mutants showed them to have reduced antibiotic susceptibility without overexpression of the SmeDEF efflux pump. Single nucleotide polymorphisms (SNPs) were found in the mutants, including one in a gene encoding a hypothetical membrane transporter and one encoding PhoP, and both mutants displayed a lower growth rate than the wild-type strain (339).

Table 9 provides a summary of the recent reports about the genetic analysis of antimicrobial resistance mechanisms used by *S. maltophilia*. Gene transfer, genetic rearrangements, and mutation events all contribute to the multidrug resistance of this opportunist.

Surveillance studies. The reporting of surveillance studies is warranted worldwide to allow us to track the emergence of new drug resistance determinants in *S. maltophilia* isolates. Resistance to cell wall synthesis inhibitors, including TMP-SMX, ceftazidime, β-lactams, and carbapenems, has been reported recently in clinical and environmental

TABLE 9 Recent publications reporting the genetics of *S. maltophilia* antimicrobial resistance

Antimicrobial[a]	Genetics and description	Reference(s)
β-Lactams	*bla*$_{SHV}$, *bla*$_{CTX-M-Gp1}$, *bla*$_{PER}$, *bla*$_{NDM-1}$, *bla*$_{OXA1-like}$, bla$_{OXA48-like}$ *bla*$_{L1,L2}$, *mrc*A, lytic transglycosylase D1, CreBC two-component system, AmpNG-AmpD$_1$-NagZ-AmpR circuit, NagZ-dependent and NagZ-independent mechanisms, and mutation of TonB gene	174, 177, 178, 296–301, 343
Aminoglycosides	*aac(6′)-Iak* and proteases *clpA* and *htpX*	303, 304, 308
Quinolones	*qnr*A, *qnr*B, *qnr*S, *oqx*A, *oqx*B, Sm*qnr* genes, *aac(6′)-Ib-cr*, *aadA2*, and mutation of *smeT*	178, 294, 295, 308, 324, 331, 348, 346
TMP-SMX	Class 1 integrons, *dfrA*, *sul*1, and *sul*2 genes	178, 307, 309, 310, 340, 341, 346
MDR efflux pumps		
ABC family		
Aminoglycosides, macrolides, polymyxins	MacABCsm (*macRS-macABCsm* cluster)	311
Fluoroquinolones, tetracycline	SmrA (*smrA*)	315
MFS family		
Erythromycin, nalidixic acid	EmrCABsm (*emrRCABsm*)	316
Fluoroquinolones, paraquat	MfsA (*soxR-mfsA* system)	317–319
RND family		
Quinolones, β-lactams, aminoglycosides	SmeABC (*smeABC*)	320, 326
Quinolones, tetracycline, chloramphenicol, TMP-SMX, macrolides	SmeDEF (*smeT-smeDEF* system, association with the *smeRySy* operon and *smeYZ*)	294, 295, 321–323, 325, 326, 331, 334
Quinolones, macrolides, chloramphenicol, polymyxin B, tetracycline, some β-lactams	SmeGH (*smeGH*, *tolCsm*, mutations of *smeH*)	292, 313
Ciprofloxacin, levofloxacin, minocycline, tetracycline	SmeIJK (*smeIJK*, association with *smeZ*)	327, 328
Nalidixic acid, doxycycline, macrolides, aminoglycosides, chloramphenicol, TMP-SMX	SmeOP-TolC (*tolCsm-pcm-smeRo-smeO-smeP cluster*)	312, 314
Quinolones, tetracycline, chloramphenicol	SmeVWX (*smeRv-smeVWX* system, association with vitamin K$_3$, inducers)	294, 329–331, 338
TMP-SMX, aminoglycosides	SmeYZ (*smeYZ*, association with *smeRySy* system, association with *smeJK*, inducers, association with *rplA* mutation)	327, 332–334, 338
Fusaric acid	FuaABC (*fuaR-fuaABC*)	336
Biocides	*qacK*, *qacL*, biocide binding to SmeT, relationship with fitness cost	307, 339

[a]TMP-SMX, trimethoprim-sulfamethoxazole; MDR, multidrug resistant; ABC family, ATP-binding cassette (ABC) superfamily; MFS family, major facilitator superfamily; RND family, resistance-nodulation-division superfamily.

isolates in Brazil (177, 340), environmental isolates in Portugal (174), and clinical isolates in China (341, 342), South Korea (343), India (344), Hungary (345), Iran (346), and Lebanon (347). Quinolone resistance has been reported in clinical isolates in Japan (348) and Greece (349) and in environmental isolates in Brazil (178). Tigecycline resistance has been reported in clinical isolates in China (350). Class 1 integrons and plasmids bearing resistance genes against cell wall synthesis inhibitors and quinolones indicate the possibility for horizontal gene transfer (177, 178, 340, 341, 346, 348, 349).

Surveillance studies across years can reveal trends in antimicrobial resistance, for example, in the resistance to TMP-SMX. A study of 300 clinical *S. maltophilia* isolates in China showed significant increases in resistance between 2005 to 2009 and 2010 to 2014, with an increase from 29.7% to 47.1% for TMP-SMX and an increase from 28.9% to 52.3% for ceftazidime; multidrug resistance (most often to minocycline, TMP-SMX, and ceftazidime) also increased from 11.0% to 31.0% during the two time periods (342). In another study of 400 clinical *S. maltophilia* isolates in China, resistance to TMP-SMX was associated with multidrug resistance (341). In a retrospective study of 579 *S. maltophilia* isolates recovered during 2008 to 2017 in Hungary, resistance to TMP-SMX was detected significantly more frequently among inpatients, and extensive drug resistance (to TMP-SMX, levofloxacin, amikacin, COL, and tigecycline) was also observed (345). The data of these studies support the need for continued efforts to develop new therapies against this pathogen.

As indicated earlier in the review, *S. maltophilia* is an environmental organism. Recent surveillance studies have shown that this bacterium carries drug resistance in nature such as in river water (174) and soils, including those used for crops important for animal feed (177, 178).

In summary, it is important to monitor antimicrobial resistance in and outside the hospital, to control the spread of drug-resistant bacteria within susceptible human populations. In addition to judicial use of antimicrobials to treat infections, controlling the disposal of antibiotics and other biocides into water supplies, other aquatic environments, and soils will limit the potential for the spread of antimicrobial resistance among other organisms, including humans.

Motility

Attachment of a pathogen to a surface is needed for colonization. Flagella are virulence factors of *S. maltophilia*, and cells display single or multiple polar flagella used for adherence. *S. maltophilia* flagella enable adherence to mouse tracheal mucus (351). *In vitro* on polystyrene, the high-affinity attachment of purified *S. maltophilia* flagellin is inhibited by anti-flagellin antisera in a dose-dependent manner (352). These findings indicate that flagella are important for the early stages of adherence of *S. maltophilia* to surfaces.

S. maltophilia flagellin induces a specific host immune response; the flagellin is distinct from *P. aeruginosa* or *Burkholderia cepacia* flagellin (353). BALB/c mice instilled with *S. maltophilia* flagellin and then exposed to *S. maltophilia* 4 h postinstillation exhibited significantly increased levels of proinflammatory cytokines (IL-1β and TNF-α) and IL-10. Myeloperoxidase and malondialdehyde levels in the mouse lungs increased post-flagellin instillation and post-bacterial instillation, and the nitric oxide level increased post-bacterial instillation. Flagellin instillation increased the number of neutrophils, lymphocytes, and monocytes in bronchoalveolar lavage fluid and also provided nonspecific protection for the mice against challenge with *S. maltophilia* and *S. aureus* (354). In another study, delivery of wild-type *S. maltophilia* SM111 and an isogenic Δ*fliI* mutant by aerosol into DBA/2N mice resulted in a significantly higher level of TNF-α in lungs early postexposure for the wild type than for the mutant (355). These studies demonstrate the immunogenicity of flagellin in the host and suggest potential use for flagellin in protection against *S. maltophilia* infection.

Flagellum expression and motility of *S. maltophilia* are tightly controlled and influenced by the bacterium's external environment. The regulation of flagellar gene expression involves c-di-GMP and FleQ, an enhancer-binding protein (356). Swimming motility and membrane stability are regulated through the expression of the CreBC two-component system and CreD, an inner membrane protein (357, 358). CreD is involved in the σ^E-mediated envelope stress response (358). *In vitro* twitching motility of clinical *S. maltophilia* strains is significantly higher under iron-depleted conditions (359). Further work is required to see if twitching motility is similarly affected *in vivo* and, if it is, to determine the impact it has on virulence of this pathogen.

The contribution of *S. maltophilia* flagella to virulence is in the early stages of bacterial adherence to surfaces. Similar to observations for the flagella of *P. aeruginosa* during chronic CF lung infection progression, *S. maltophilia* flagella may be unnecessary in the later stages of CF lung infection (360). Decreased *S. maltophilia* motility over time has been observed during the progression of chronic CF lung infection (260). As flagella are immunogenic, the loss of flagella could benefit *S. maltophilia* by reducing its exposure to the host immune defenses.

Adherence, Colonization, and Persistence

Adherence and colonization of a surface enable *S. maltophilia* to form biofilms during infection and disease. A recent study has shown that the adherence of *S. maltophilia* Sm2 to abiotic (polystyrene) and biotic (mouse tracheal mucus, mouse trachea, and Hep-2 cells) surfaces is influenced by type of culture media, oxygen concentrations, and pH (361). These observations are not surprising given the genetic

heterogeneity and subsequent diversity of cell surface structures (lipopolysaccharide [LPS], OMPs, flagella, pili, etc.) expressed by different strains of this opportunist in various environmental niches. GpmA, a glycolytic enzyme phosphoglycerate mutase, has been recently identified as a mediator of the early stages in adherence of *S. maltophilia* to polystyrene and to immortalized CF-derived bronchial epithelial cells (362). Research is needed to identify whether GmpA is localized on the cell surface of *S. maltophilia*.

In host. Colonization of *S. maltophilia* is integral to the pathogen's ability to persist and damage the susceptible host. In a study of adult patients colonized with multidrug-resistant Gram-negative bacilli, including *S. maltophilia* following single cord blood transplantation, a multivariate analysis showed that persistence of these pathogens significantly increased nonrelapse mortality and development of bloodstream infection (363).

The genetic heterogeneity of *S. maltophilia* strains may be reflected in their ability to replicate and persist in mouse strains (364). Variation in replication and persistence of *S. maltophilia* can be seen with clinical strains in A/J mice. The strain of mouse chosen for study of pathogenesis is important, as demonstrated by observed differences in replication of *S. maltophilia* K279a among mouse strains (A/J, BALB/c, C57BL/6, and DBA/2) (364). Further research is needed to determine whether specific mouse strains are more appropriate than others in the animal models of different *S. maltophilia* infections.

Contact lenses. *S. maltophilia* has been recovered from contact lens storage cases. Several recent studies have examined contact lens materials, lens cases, disinfectant solutions, presence of organic materials, and their impact on *S. maltophilia* cell adherence, viability, persistence, and biofilm formation (365–373).

The adherence of *S. maltophilia* ATCC 17676 on contact lenses of hydrogel material (etafilcon A, ACUVUE 2; Johnson & Johnson Vision) and silicone hydrogel (senofilcon A, ACUVUE OASYS; Johnson & Johnson Vision) has been studied in the absence or presence of an artificial tear solution (365). On senofilcon A, in the presence or absence of artificial tear solution, this *S. maltophilia* strain exhibited significantly decreased viability compared to that on etafilcon A. More work is needed to assess the efficacy of these materials against multiple clinical *S. maltophilia* strains.

Stable organoselenium polymer has demonstrated good potential for its use as a component of lens case material. Organoselenium polymer significantly reduced (7.5 log) *S. maltophilia* ATCC 13637 CFU/cm^2 of biofilm, and as low as 0.1% organoselenium inhibited biofilm formation (366). Studies are needed to test this material against more *S. maltophilia* strains, and it remains to be seen whether the presence of organic material exhibits interference with the antibiofilm activity of this polymer.

The results of a recent study indicate that attention should be paid to which temperature and culture medium are being used to recover bacteria from biofilms in contact lens cases (367). The number of viable *S. maltophilia* ATCC 17676 biofilm cells recovered from Sight Savers contact lens cases (Bausch & Lomb) was higher at 32°C than with incubation at 37°C, and the recovery of *S. maltophilia* was significantly higher on Columbia agar with 5% sheep's blood than on other tested agar media (367). Thus, the incubation environment is important to consider when assessing the efficacy of cleaning solutions for contact lens cases.

Multipurpose disinfecting solution 3 (MPDS-3) COMPLETE RevitaLens (polyquaternium-1 plus alexidine dihydrochloride plus EDTA), and MPDS-4 Biotrue (polyquaternium-1 plus polyhexamethylene biguanide [PHMB] plus EDTA) have shown efficacy against *S. maltophilia* isolated from lens cases, separately reducing counts $\geq$4 $\log_{10}$ after 6 h of exposure and $\geq$4 $\log_{10}$ after 14 days of exposure (368). As this was a relatively small study, larger studies are need to further assess these solutions. Povidone iodine (PI) (50 ppm active iodine) has also demonstrated efficacy against biofilms of *S. maltophilia* strains ALC01 and UD14 containing 10^7 to 10^8 CFU, with $<$10 CFU recovered postdisinfection (369). These studies underscore the importance of adequate disinfectant solutions to maintain clean contact lenses.

Recent studies have investigated the presence of organic materials and the adherence, survival, and biofilms of bacterial contaminants on contact lenses (370–372). In the presence of one of four contact lens care solutions, Biotrue (Bausch & Lomb; active ingredients, 0.00013% polyaminopropyl biguanide, 0.0001% polyquaternium, hyaluronan, poloxamine, boric acid), PureMoist (Alcon Laboratories; active ingredients, 0.001% polyquaternium-1, 0.0006% myristamidopropyl dimethylamine, Tetronic 1304, HydroGlyde moisture matrix, boric acid), ClearCare (Alcon Laboratories; active ingredients, 3% hydrogen peroxide, Pluronic 17R4), and PeroxiClear (Bausch & Lomb; active ingredients, 3% hydrogen peroxide, poloxamer 181, carbamide, and propylene glycol), on Lotrafilcon B soft contact lenses containing RPMI medium and neutrophils, *S. maltophilia* ATCC 13637 demonstrated a 9-log to 10-log reduction. Confocal microscopy and LIVE/DEAD BacLight staining showed the presence of nonviable bacteria and extracellular debris on the lens after cleaning with the lens solutions (370). The incubation of contact lenses in inoculum with 10% organic soil has been reported to significantly increase the adhesion of two strains recovered from lens cases, *S. maltophilia* 006 and *S. maltophilia* 002, to the lens surface (372). The presence of neutrophil-derived debris accelerates *S. maltophilia* biofilm formation on contact lenses, resulting in denser biofilms with higher CFU counts (371). *S. maltophilia* Xmal10, a strain from a contact lens wearer, has been shown to bind lactoferrin. Lactoferrin found in mucosal fluids did not kill but instead induced siderophore production by this strain (373). Further work is needed to determine if lactoferrin contributes to and favors the persistence of *S. maltophilia* strains. Together these observations indicate that organic material present can influence pathogen colonization and biofilm formation on contact lenses.

Implants. The type of material used in implants is important when the goal is to prevent the colonization of biofilm-forming bacteria. A fluorine-phosphorus-doped titanium alloy shows promise for use in the prevention of bacterial colonization of orthopedic implants (374). The adhesion and viability of *S. maltophilia* ATCC 13637 decreased significantly by 80% and 47%, respectively, on bottle-shaped TiO_2 nanotubes samples of Ti-6A1-4V alloy. The alloy is compatible with osteoblastic cell proliferation and matrix mineralization. The precise mechanism of bactericidal toxicity of the released aluminum from this alloy remains to be determined. Future research needs to include more *S. maltophilia* strains to discern if there are any strain-specific effects and to determine the viability of this technique in different orthopedic applications.

Water systems. *S. maltophilia* is a common contaminant of drinking water. Its presence has been confirmed in drinking water distribution systems as well as in other freshwater and marine environments. Chemical and physical methods are being assessed for their reduction of microorganisms present in drinking water distribution systems (164, 167, 168). A recent study has shown that NaOCl (0.5 mg/liter) treatment of *S. maltophilia* biofilms increased resistance to removal by mechanical stresses and that a combination treatment of NaOCl with mechanical stress did not improve biofilm removal (164). Copper alloys (57%, 96%, and elemental) significantly inhibited *S. maltophilia* biofilm formation, and combination treatment (free chlorine at 10 mg/liter for 10 min and shear stress of 1.5 m/s for 30 s) significantly reduced viable biofilm bacteria on the 57% copper alloy surface (167). The choice of treatment of water must consider possible shifts in microbial populations that occur as a result of treatment. Exposure of wastewater to artificial solar radiation resulted in increased relative abundance of ciprofloxacin- and rifampin-resistant bacterial communities containing solely multidrug-resistant *S. maltophilia* (163). The antimicrobial activity of photocatalytic gadolinium (Gd)-doped TiO_2 nanoparticles against one strain of *S. maltophilia* shows promise for use in wastewater treatment (375). Gd-doped TiO_2 nanoparticles at concentrations of 0.1 and 1 mol% reduced cell survival after 12 h of exposure to visible light, with $>$97% cell inactivation. The toxicity of these nanoparticles against eukaryotic cells needs to be assessed. Further research using additional *S. maltophilia* environmental strains may help reveal the exact mechanism of action of these nanoparticles. *N*-Acetyl-L-cysteine-grafted siloxane polymer may have potential as antimicrobial and antibiofilm materials in industrial water distributions systems (171). Exposure to the polymer

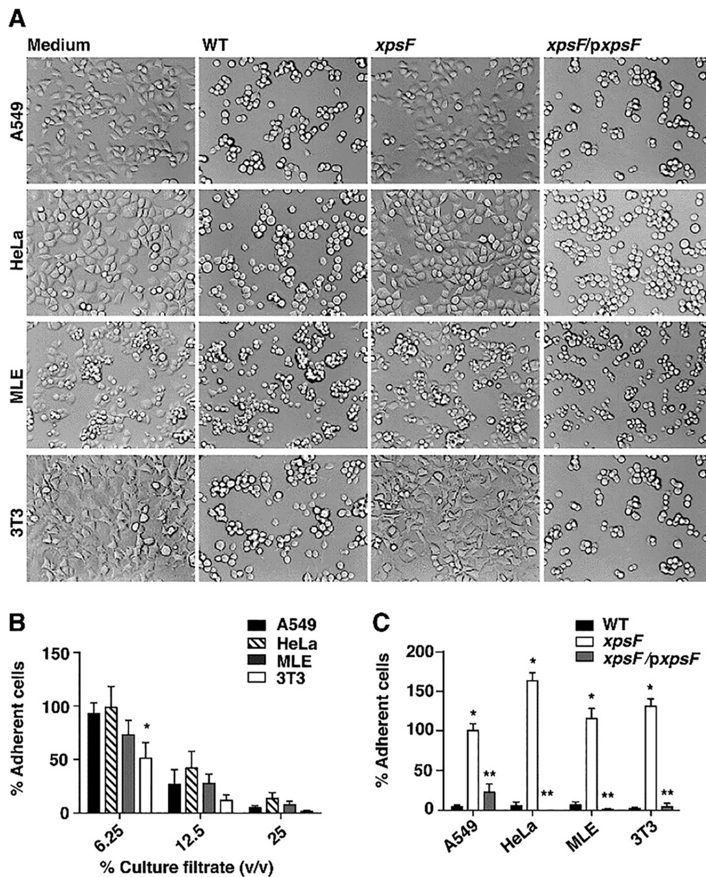

FIG 2 Effect of WT and Xps mutant supernatant on various human and murine cell lines. (A) The A549, HeLa, MLE, and 3T3 cell lines were incubated for 3 h with 25% (vol/vol) supernatants from strain K279a (WT), the *xpsF* mutant NUS4 (*xpsF*), the complemented *xpsF* mutant (*xpsF*/p*xpsF*), or a medium control. Mammalian cell morphology was evaluated by phase-contrast light microscopy. Data are representative of three independent experiments. (B) Cell lines were incubated with WT supernatant at the indicated doses for 3 h and washed, and then the remaining adherent cells were quantified by measuring absorbance at OD_{600}. Data were normalized to the value for cells treated with medium alone, which was set at 100% adherence. An asterisk indicates a statistically significant difference from A549 and HeLa cells ($P < 0.05$). (C) Cell lines were incubated for 3 h with 25% (vol/vol) supernatants from the WT, the mutant, and the complemented mutant. Cell detachment was determined as described for panel B. Single and double asterisks indicate statistically significant differences from the WT and the *xpsF* strain, respectively ($P < 0.05$). For panels B and C, data are means and standard errors of the means (SEM) from three independent experiments. (Figure reproduced and legend adapted from reference 379 with permission.) OD_{600}, optical density at 600 nm.

(at 0.25% concentration) resulted in significant reduction of adhesion (>96% as determined by luminometry assay) of *S. maltophilia* to glass (171). More research is needed to determine the effect of the polymers on the growth inhibition, biofilm formation, and elimination of established biofilms of *S. maltophilia*.

Protein Secretion Systems

Xps type II secretion system. Type II protein secretion systems have been identified in several human pathogens as important virulence factors contributing to pathogenesis. The type II system enables a Gram-negative bacterium to secrete proteins into its external environment. A recent review has examined the role of type II secretion in Gram-negative bacteria (including *S. maltophilia*), their secreted proteins, and effects on host cells (376). The *S. maltophilia* Xps type II secretion system is required for secretion of caseinolytic and gelatinase activity. It mediates the secretion of serine proteases, StmPr1, StmPr2, and StmPr3, resulting in actin rearrangement, rounding, and detachment of A459 lung epithelial cells *in vitro* (Fig. 2) (377–379). These proteases

degrade extracellular matrix proteins and cytokine IL-8 (378, 379). StmPr1 is the major player in lung cell damage, with its degradation of fibronectin, fibronectin receptor integrin $\alpha 5\beta 1$, collagen, E-cadherin, and occludin and through cleavage of PAR1 and PAR2 proteins, recruiting neutrophils (378). When human CFEB41o- bronchial epithelial cells are challenged with *S. maltophilia* K279a culture supernatants, the effects of serine proteases are similar to the morphological changes seen in A459 cells and include disruption of the epithelial cell barrier and degradation of tight junction proteins ZO-1 and occludin (380). Clinical *S. maltophilia* isolates show various degrees of expression of the Xps type II secretion system, suggesting that this system may promote spread of *S. maltophilia in vivo* resulting in host lung damage (377). Taken together, these studies underscore the significant roles of cell damage and disruption of the immune system that proteases play as virulence factors against the susceptible host infected by *S. maltophilia*. Further work is needed to determine if pharmaceutical strategies can block the activities of these proteases without disrupting normal host cell function.

VirB/D4 type IV secretion system. A VirB/D4 type IV secretion system is conserved among *S. maltophilia* strains, and it mediates the killing of human and bacterial cells, inhibiting apoptosis of A549 cells and primary human bronchial/tracheal epithelial cells (ATCC PCS-300-010) in a contact-dependent manner (381). Transwell experiments have indicated that this secretion system caused the death of *P. aeruginosa* strains 7700, PAO1, and PAK in a contact-dependent manner. This manner of killing by *S. maltophilia* did not extend to all *Pseudomonas* species. Further work is needed to elucidate the reasons for this limited killing of particular susceptible bacteria. These studies may provide insights for new pharmacological intervention of infections caused by *P. aeruginosa*. The disruption and killing of *P. aeruginosa* in a polymicrobial infection with *S. maltophilia* could ease the host immune system's ability to clear the infection. Recently, *S. maltophilia* K279a has been shown to induce death in several Gram-negative bacteria (*E. coli*, *P. aeruginosa*, *Klebsiella pneumoniae*, and *Salmonella enterica* serovar Typhi) in a type IV secretion system-dependent manner, and secreted effectors from one species can be recognized by other species and translocated using the other species' type IV secretion system (382). The conservation of the type IV secretion system machinery across different bacteria is expected, as these microbes compete for space and nutrients.

Iron

S. maltophilia has been reported to produce catecholate siderophores (383–386) for scavenging iron from its external environment. Iron is important for *S. maltophilia* biofilm formation, oxidative stress response, and virulence (387). Under iron-restricted conditions, compared to its parent, *S. maltophilia* K279a, an isogenic spontaneous *fur* mutant, formed thinner biofilms with greater superoxide dismutase activity; the *fur* mutant also exhibited greater virulence than K279a against *G. mellonella* larvae (387). *S. maltophilia* produces a catecholate siderophore, stenobactin, and the *fepA* gene equivalent (RS06850) encodes a siderophore receptor (384). *S. maltophilia* strains K279a, R551-3, D457, and JV3 contain iron uptake mechanisms that include the iron siderophore sensor and receptor system and the heme, hemin uptake, and hemin transport system (385). Siderophore production is dependent on the *entAFDBEC* operon, and heme uptake is controlled by *hgbBC*; *S. maltophilia* strains can use iron sources, including ferric iron, hemoglobin, lactoferrin, and transferrin, for growth (388). The details of these uptake mechanisms have been presented in a recent review (388). The importance of iron acquisition in virulence is highlighted by a recent study in which a clinical strain (CS17) displayed significantly higher siderophore secretion and killed higher numbers of nematodes under iron-restricted conditions than environmental strain LMB959; in a comparison of iron-responsive proteins in these strains, CS17 also exhibited higher expression of iron acquisition proteins than strain LMB959 (386). Future work is needed to elucidate the roles of various iron-responsive proteins in *S. maltophilia* pathogenesis.

The *ampI* and *ampR* genes of *S. maltophilia* are involved in iron transport (389, 390). The *ampI* gene encodes an iron exporter that enables the pathogen to reduce

β-lactam-induced stress, with significantly increased expression upon exposure to β-lactams (390). AmpR, a regulator of β-lactamase expression, has recently been shown to regulate iron depletion-mediated synthesis of the siderophore stenobactin, with increased expression of *ampR* in cells under iron-restricted conditions and exposed to β-lactams (389).

In summary, there are several mechanisms used by *S. maltophilia* to acquire and use iron. The homeostatic control of iron within the bacterial cell is also noted through observations of the cells when exposed to antimicrobials.

Outer Membrane

The outer membrane of *S. maltophilia* contributes to the antimicrobial resistance of this pathogen and pathogenesis. *S. maltophilia* outer membrane vesicles (OMVs) contribute to antibiotic resistance (391) and biofilm formation (392) and stimulate expression of host defenses (393). Outer membrane proteins (OMPs) of *S. maltophilia* have demonstrated protective ability against this pathogen (191, 394, 395). Increased outer membrane permeability of *S. maltophilia* increases the susceptibility of this pathogen to aminoglycosides, macrolides, SDS, and bile salts (1, 396). Proteomic analyses are ongoing to compare OMVs and outer membrane proteins (OMPs) across *S. maltophilia* strains and identify proteins used in virulence, antimicrobial resistance, and pathogenesis (397). From these studies, it is clear that the outer membrane of *S. maltophilia* is multifunctional and that it plays a key role in the success of this opportunist.

Outer membrane vesicles and outer membrane proteins. The secretion of outer membrane vesicles may be an indirect form of communication for the pathogen with other bacteria. The secretion of outer membrane vesicles (OMVs) by *S. maltophilia* is stimulated by imipenem, by diffusible signal factor (DSF) from *S. maltophilia* and, to a lesser degree, *Burkholderia cenocepacia* DSF, and by ciprofloxacin (392, 398). Proteomic analysis demonstrated that the *S. maltophilia* OMVs contained two Ax21 proteins, Smlt0387 and Smlt0184 (392). The OMVs can package the active β-lactamases of *S. maltophilia*, leading to degradation of β-lactams in the external milieu surrounding the bacteria and subsequently increasing the MIC needed against cocolonizing pathogens (391). Commonly used antibiotics against *S. maltophilia* infections should be tested for their effect on OMV secretion by this pathogen, as this will help us better understand the interactions these OMVs may have with other microbial species found in polymicrobial infections.

The OMVs of *S. maltophilia* generate host inflammatory responses *in vitro* and *in vivo* (393). Cytotoxicity effects have been observed for A549 epithelial cells when exposed to *S. maltophilia* OMVs, and OMVs induce visible inflammation and increased expression of IL-1-β, IL-6, IL-8, monocyte chemoattractant protein 1 (MCP-1), and TNF-α in BALB/c mouse lung tissues (393). Further research will discern whether OMVs of *S. maltophilia* transport other molecules/compounds that contribute to the pathogenesis of this organism.

The OMPs of *S. maltophilia* contribute to adherence and cell susceptibility to stresses and can provide hosts with protection against this pathogen (191, 394, 395, 399). OMP MopB, for example, is important for adherence to glass, virulence toward L929 fibroblasts, exposure to SDS and hydrogen peroxide, and protection against serum-mediated killing (399). Vaccination with OMPs from an *S. maltophilia* strain along with natural adjuvants, including propolis (Pro), *Ficus carica* polysaccharide (Fcps), and glycyrrhizin (Gly), have provided protection for channel catfish against this pathogen (191). Further research using various clinical and environmental *S. maltophilia* would reveal any possible strain differences that may affect vaccine efficacy. Immunization with recombinant OMP Smlt4123 has been reported to protect BALB/c mice against early development of bacteremia following intraperitoneal challenge with *S. maltophilia* (395). Immunization with recombinant outer membrane protein A (rOmpA) has been shown to protect C57BL/6 mice against *S. maltophilia* infection; immunized mice exhibited significantly higher serum levels of IgG, IgA, IgG1, and IgG2a, indicating a systemic humoral immune response, and higher levels of IFN-γ, IL-2, and IL-17A levels,

reflecting a cellular immune response. Significantly reduced bacterial loads and significantly reduced TNF-α and IL-6 levels in bronchoalveolar lavage fluid (BALF) were observed in the immunized mice. Together, these studies highlight the promise of OMPs as vaccine candidates against *S. maltophilia*.

Biofilms

Antimicrobial resistance. A significant feature of *S. maltophilia* is its ability to form biofilms on moist surfaces (1). The antimicrobial resistance of biofilm cells is typically greater than that of planktonic cells. *S. maltophilia* strains are typically resistant to a wide range of antimicrobials, and the added formation of biofilm increases their resistance to antimicrobial challenge (400). A recent study has proposed that biofilm formation by *S. maltophilia* may provide a mechanism for planktonic cells to resist antimicrobials that would otherwise be deleterious (401). This study also suggested that diagnostic testing of *S. maltophilia* clinical strains include assessment of their biofilm-forming ability and stresses the need for developing an antimicrobial testing protocol for biofilms (401). As there are still no globally accepted cutoffs used in the testing of some antimicrobials against *S. maltophilia*, it is urgent to have antimicrobial testing against biofilms standardized, as new drug and drug combinations are being developed to combat biofilm infections.

Horizontal gene transfer activity has been shown to be greater in biofilms than among planktonic cells, and plasmids are effective vehicles for antimicrobial resistance gene transfer (402). When considering the antimicrobial resistance of the *S. maltophilia* biofilms, one can look across at the biofilms of a cocolonizer, *P. aeruginosa*. The continuous-flow biofilms of *P. aeruginosa* have shown that this bacterial pathogen is capable of natural transformation of chromosomal and plasmid DNA aided by type IV pili (403), and it is tempting to speculate that similar gene transfers that mobilize drug resistance determinants are occurring within the safe haven of an *S. maltophilia* biofilm. *S. maltophilia* biofilm formation is also sensitive to environmental conditions, for example, culture medium composition and temperature (1, 140). Strategies to inhibit biofilm formation or reduce established biofilms are discussed below.

***S. maltophilia* behavior in mixed biofilms.** *S. maltophilia* is often found *in vivo* as a member of polymicrobial communities. Recent studies of biofilms formed by *S. maltophilia* with other microbes have increased our awareness of the interactions that occur between these organisms (162, 404, 405). As *S. maltophilia* can cocolonize with other pathogens in susceptible hosts, it is important to study the interactions of this opportunist with other organisms in multispecies biofilms. *S. maltophilia* and *P. aeruginosa* both colonize the lung environment. Recent work has examined more closely the interplay of these two pathogens during biofilm development (60, 404, 406, 407). Expression of *S. maltophilia* regulator element SmoR is induced by acyl homoserine lactones (AHLs) of *P. aeruginosa*, resulting in increased swimming motility and high cell density (406). Additional research will elucidate whether SmoR responds to other AHLs or cellular molecules produced by additional bacterial pathogens colocalized with *S. maltophilia*. *In vitro*, the adherence of *S. maltophilia* to catheter surfaces may result in improved subsequent attachment and biofilms of other pathogens such as *P. aeruginosa* and *Acinetobacter baumannii* (404). In *in vitro* mixed cultures of CF strains, *S. maltophilia* has exerted several effects on *P. aeruginosa*, significantly reducing its production of extracellular polymeric substance, significantly inhibiting its swimming motility and adhesion to CFBE41o- cells, increasing *P. aeruginosa* expression of *aprA* (encodes a protease) and *algD* (encodes alginate), and decreasing expression of *rhlR* and *lasI* (quorum-sensing-related genes) while not altering cell viability (407). In turn, *P. aeruginosa* has adversely impacted planktonic cells and reduced the cell viability of *S. maltophilia*. Interestingly, in the mixed-culture biofilm, a CF *S. maltophilia* strain exhibited less susceptibility than *P. aeruginosa* to tobramycin (407). Similar results were obtained in dual biofilms, where *S. maltophilia* was less susceptible to ciprofloxacin than *P. aeruginosa* (408).

The interactions of *S. maltophilia* and *P. aeruginosa* in biofilms are intriguing. In *in vitro* dual-species biofilms of chronic CF *S. maltophilia* strains with *P. aeruginosa*, *S. maltophilia* has

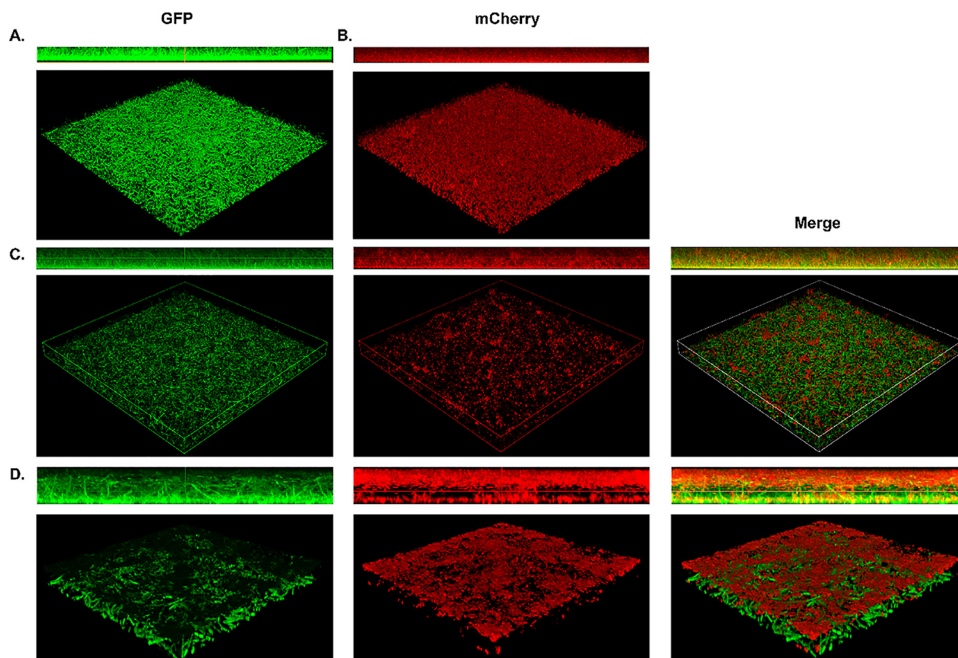

FIG 3 *S. maltophilia* and *P. aeruginosa* stratify within polymicrobial biofilms *in vitro*. Structural composition of polymicrobial biofilms was assessed via confocal imaging of *S. maltophilia* K279a (GFP+), *P. aeruginosa* mPA0831 (mCherry+), or both grown at 30°C for 8 h. Single-species biofilms of *S. maltophilia* K279a (GFP+) (A) and *P. aeruginosa* mPA0831 (mCherry+) (B) were imaged at ×40 magnification. Dual-species foci were imaged at ×40 magnification (C) and zoomed 4× for a total magnification of ×160 (D). (Figure reproduced and legend adapted from reference 60 with permission.)

formed the base of the biofilm, with *P. aeruginosa* situated as a layer above *S. maltophilia* (Fig. 3) (60). In mouse respiratory coinfections of *P. aeruginosa* and *S. maltophilia*, significantly increased numbers of *S. maltophilia* cells were present and colocalized with alginate in the lungs. Delayed clearance of *S. maltophilia* from the coinfected mice was also noted (60).

In summary, from the studies described, it appears that *S. maltophilia* provides the stable surface support for *P. aeruginosa* adherence and that *P. aeruginosa* can provide a means for the persistence of *S. maltophilia*, resulting in a persistent and flourishing coinfection. The mechanism used by *P. aeruginosa* that enables the persistence of *S. maltophilia* is currently unclear. Such cooperative and organized behavior of these two pathogens requires further study to elucidate the molecular mechanisms used in this dual-species collaboration and to see whether, from an antibiofilm therapy standpoint, it is possible to disrupt the delivery and receipt of cellular signals without damage to the infected host.

Culture conditions can affect the interactions of microbes. *In vitro* studies of *S. maltophilia* with *E. coli* K-12 PHL644 under continuous flow conditions showed that attachment of *S. maltophilia* cells to the flow cell surface improved *E. coli* biofilm formation; however, under static batch culture conditions, *S. maltophilia* impeded *E. coli* biofilm formation (162). Future research is needed to determine if *S. maltophilia* affects other bacterial pathogens within mixed culture biofilms in a similar manner and to identify *S. maltophilia*-specific cellular components that contribute to the adherence of the other pathogen.

Aspergillus fumigatus is another microbe that can be found in the human respiratory tract (405). In mixed biofilms of *A. fumigatus* ATCC 13073 and *S. maltophilia* ATCC 13637, *S. maltophilia* exhibited antagonistic activity against *A. fumigatus* through changes in fungal structure, such as modification of hyphae, a less dense hyphal network, significantly delayed growth of the fungus hyphae, thicker cell walls of *A. fumigatus*, and a

thinner biofilm (405). Clinical (human and animal) and environmental strains of *S. maltophilia* have been observed to exhibit different antagonistic effects against *A. fumigatus*, and bacterial strain-dependent effects were also observed in virulence against the *in vivo* model *G. mellonella* (409). Future research is needed to elucidate the exact mechanism(s) imposed by *S. maltophilia* on *A. fumigatus*.

In recognition of the interactions occurring between *S. maltophilia* and other microbes in mixed-culture biofilms, work is needed to understand how genetic mechanisms in these organisms are regulated during biofilm development and within mature biofilms. A recently developed multichannel microfluidic biosensor platform enables users to monitor, in real time, the gene expression of cells within biofilms formed in the system (410). This platform may provide an attractive method to monitor mixed-culture biofilms in real time using simulated CF conditions.

Genetics. The genetic regulation of biofilm development by *S. maltophilia* is complex. There are several mechanisms of control at the transcriptional level of gene expression. FsnR (flagellum biosynthesis regulator) is a transcriptional regulator that activates transcription of several flagellum-associated genes and mediates biofilm formation (411). BsmR (biofilm and swimming motility regulator), an EAL domain-containing response regulator, is a positive regulator of swimming motility and positively regulates *fsnR* expression (412). Transcription factor BsmT mediates expression of BsmR through a positive feedback mechanism (412). BfmA, a positive transcriptional regulator, controls *S. maltophilia* biofilm development through regulation of the BfmA-BfmK operon (encodes a two-component signal transduction system containing Smlt4209 [*bfmA* encodes a biofilm activator] and Smlt4208 [*bfmK* encodes a biofilm activator cognate kinase]) and expression of Smlt0800 (*acoT* encodes an acyl coenzyme A [acyl-CoA] thioesterase) (413). Identification of molecular mechanisms that are shared across various clinical *S. maltophilia* strains and unique to *S. maltophilia* can provide possible targets for pharmaceutical intervention.

DSF system and quorum sensing. A diffusible signal factor (DSF) was identified as a cell-cell signaling molecule present in *Xanthomonas campestris* pv. *campestris* (414). *S. maltophilia*, previously classified as *Xanthomonas maltophilia* (16), produces DSF that is encoded by the *rpf* gene cluster (415). A *S. maltophilia rpf* mutant was reported as unable to produce DSF (415). However, this paper was retracted due to errors in data presentation (416). The DSF molecule produced by *S. maltophilia* has been identified as *cis*-11-methyl-2-dodecanoic acid (417, 418).

The influential role of *rpf* (regulation of pathogenicity factors) was evident in a study of the interaction of *S. maltophilia* with oilseed rape plants (419). The DSF quorum-sensing system improved the plant colonization of *S. maltophilia* and growth of the plants. FISH and confocal microscopy confirmed organized colonization and biofilm formation of wild-type *S. maltophilia* in contrast to the diffuse scattered arrangement of *rpfF* mutant cells and formed biofilm. The *rpf*/DSF system influences multiple genes used in colonization of the plants, including those involved in motility, LPS, biofilm, iron acquisition, antimicrobial sensitivity, and stress resistance. In the *rpfF* mutant, genes used in synthesis and export of spermidine were downregulated (419). The importance of *rpf* for virulence was demonstrated when an *S. maltophilia* K279a-derived *rpf* mutant displayed reduced virulence against *Candida albicans* (420). From these two studies, it is clear that the *rpf*/DSF system is a central player in the colonization and virulence of *S. maltophilia*.

The *rpf* gene cluster includes *rpfF* (encodes a synthase) and *rpfC* (encodes a sensor) (421, 422). In *S. maltophilia* clinical isolates, two genetically and phenotypically distinct populations of *rpfF* (*rpfF*-1 and *rpfF*-2), each associated with their respective *rpfC* variant, have been identified. Under wild-type conditions, *S. maltophilia* strain E77 carrying RpfC-RpfF-1 exhibited DSF activity, in contrast to strain M30 carrying RpfC-RpfF-2 that was unable to produce DSF (422). The RpfC-RpfF-2 complex was able to detect DSF; in the presence of the *rpf*-1 strain, the *rpf*-2 strain produced DSF, and synergy was observed when both strains were in close proximity (Fig. 4) (423). The *rpf*-2 strain also

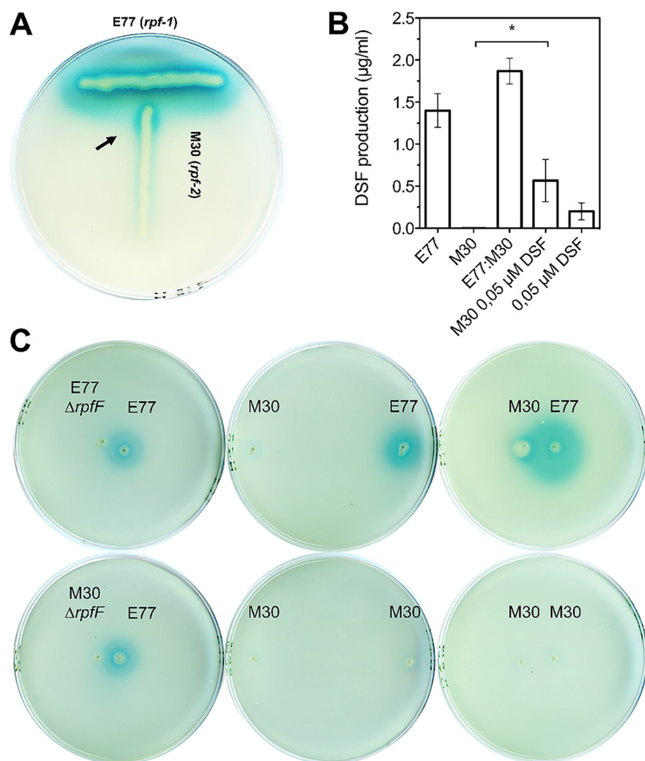

FIG 4 (A) T-seeded colony-based DSF bioassay of strains E77 and M30. Arrow indicates DSF production of M30 (*rpf-2*) strain upon detection of DSF molecules produced by E77 (*rpf-1*). (B) DSF quantification of supernatants from axenic cultures of E77 and M30, a mixed culture E77:M30 (1:1), an axenic culture of M30 supplemented with synthetic DSF at 0.05 μM final concentration and a corresponding control (equal volume of LB broth containing 0.05 μM DSF), using the microtiter DSF bioassay; *, $P < 0.05$ by one-way ANOVA and posttest. (C) Colony-based DSF bioassay of E77, M30 and their respective Δ*rpfF* mutants seeded at different distances on the same agar plate. (Figure reproduced and legend adapted from reference 423 with permission.) ANOVA, analysis of variance.

produced significant amounts of DSF in the presence of exogenous DSF. DSF production is regulated by a positive feedback mechanism. The *rpf*-1 and *rpf*-2 strains acted synergistically in a zebrafish infection model, resulting in 100% mortality and significantly high DSF production (423).

The *rpf*/DSF system of *S. maltophilia* has been reported to regulate several factors involved in virulence, motility, biofilm formation, resistance to oxidative stress, and antimicrobial susceptibility (424, 425). Isogenic *rpfF* mutants of *S. maltophilia* K279a exhibited reduced virulence, increased sensitivity to oxidative stress, decreased motility, and reduced production of protease, DNase, and lipase and displayed altered biofilm; addition of exogenous DSF restored motility and increased biofilm production (424, 425). It will be interesting to see whether the *rpf*/DSF system is mediated by other regulatory circuits. Two recent reviews explored quorum sensing in *S. maltophilia* and indicated that quorum-quenching applications had yet to be discovered (421, 426).

In summary, these studies emphasize the major role of DSF in the pathogenesis and virulence of *S. maltophilia* and increase our awareness of the importance of studying the communication between different genetic populations as well as different microorganisms in mixed-culture infections.

A recent study of the *rpf*-1 and *rpf*-2 populations in diverse clinical *S. maltophilia* isolates recovered from different geographical regions has reported important observations between the type of *rpf* variant and antimicrobial susceptibility, biofilm formation, and virulence (427). The strains of variant *rpf*-2 formed stronger biofilms and demonstrated greater virulence against *G. mellonella* larvae than strains of variant *rpf*-1. Assessment of

genotypes and virulence revealed that a link of biofilm-forming ability with genogroup C was significant. Interestingly, antimicrobial resistance appeared to correlate with *rpf* variant, as *rpf*-1 strains exhibited greater resistance to β-lactam antibiotics, while the *rpf*-2 strains demonstrated greater resistance to colistin (427). This study has demonstrated connections between *S. maltophilia* strains' molecular mechanisms of pathogenesis, genogroup, and geographical location. A larger scale study of this type would provide valuable information about the spread of highly virulent variant strains around the globe.

Ax21 (activator of XA21-mediated immunity) is a highly conserved, type 1, secreted sulfated outer membrane protein found in plant and animal pathogens, including *S. maltophilia* (428). Ax21 has been suggested to induce quorum sensing; though currently, its role remains unclear. A comparison of *S. maltophilia* and the effects of a mutation in *ax21* were reported (429); this study was retracted however, due to errors in data presentation (430). An Ax21-like protein in *Xanthomonas oryzae* pv. *oryzicola* was proposed to be positively regulated by DSF-mediated quorum sensing (431). A recent report indicated that Ax21 alters biofilm formation and virulence of *S. maltophilia* (432). *S. maltophilia* K279a, K279a *ax21* mutant, and the complemented mutant [strain K279a *ax21*(pSmlt0387)] were used in this study. In comparison to K279a and the complemented *ax21* mutant, the *ax21* mutant had significantly impaired motility, inhibited biofilm formation, increased susceptibility to tobramycin, and reduced virulence in the *G. mellonella* larva assay. Addition of Ax21 or AX21Y (a nonsulfatable variant of Ax21) to the *ax21* mutant was observed to restore motility (432). It may be that Ax21 is a cell signaling molecule, but this remains controversial. More work is needed to determine the role of Ax21 *in vivo* using animal models of infection.

Strategies to inhibit and eliminate biofilms. *S. maltophilia* biofilm formation can vary with surface material, availability of nutrients, and culture conditions (1). The persistence of biofilms in infection has necessitated research to find intervention strategies that prevent or inhibit biofilms from forming and/or eliminate already established biofilms.

Recent work has focused on the environments in which the biofilms are formed. The stimulation of early immature clinical *S. maltophilia* biofilms by an extremely low-frequency magnetic field (ELF-MF) resulted in strain and species ion-dependent effects, with two of the three strains tested showing an improvement in growth, and different effects were observed for biofilm biomass and biofilm viability (433). *S. maltophilia* planktonic cells and biofilms have demonstrated sensitivity to blue light (400 nm), with reductions in cell viability and biofilm-forming ability (seeding) after exposure (30 min, 108 J/cm^2) (434). Fluids used for continuous renal replacement therapy (CRRT) have exhibited variation in their ability to inhibit *S. maltophilia* NCTC 10257 growth and biofilm formation (435). CRRT fluids (monosol S, lactate-based solution [Baxter Healthcare]; Accusol 35, bicarbonate-based solution [Baxter Healthcare]; Prismocitrate, citrate-based anticoagulant [Gambro]; 4% trisodium citrate [Fresenius]; and Ci-Ca K2, bicarbonate-based calcium-free dialysis fluid [Fresenius]) were investigated. Of these fluids, Accusol 35 was the most effective in inhibiting growth, and in Accusol 35, Prismocitrate, and trisodium citrate, no biofilms were formed. Together, these studies demonstrated that the ability of *S. maltophilia* to form biofilms is mediated by its external environment.

Differences in biofilm formation have been observed for strains from different sources. In one study, comparison of biofilms formed by *S. maltophilia* CF and non-CF isolates showed that CF isolates were more sensitive to changes of temperature, CO_2 concentration, and pH (436). In another study, non-CF strains produced significantly more biofilm on polystyrene than CF strains, while CF strains demonstrated greater antimicrobial resistance (401).

Antimicrobial inhibitory concentrations are generally higher for biofilms than for planktonic cells, and this holds for *S. maltophilia* (400, 437–439). For example, in one study, tobramycin demonstrated a MIC_{90} of 1,600 μg/ml against 101 *S. maltophilia*

CF isolates in comparison to a 90% biofilm-inhibitory concentration (BIC) BIC_{90} of 3,200 μg/ml (405).

Fluoroquinolones, used in treatment of *S. maltophilia* infections, have exerted inhibitory activity against biofilm formation *in vitro* (438–440). The use of levofloxacin against CF biofilms has received some attention. Against CF patient isolates, levofloxacin at 100 mg/liter has demonstrated high effectivity against planktonic and biofilm *S. maltophilia* cultures (440). Under standard culture conditions (cation-adjusted Muller-Hinton broth at 37°C, pH 7.3, aerobiosis) and under CF-like culture conditions (synthetic CF medium at 37°C, pH 6.8, 5% CO_2), clinical *S. maltophilia* strains produced biofilms that were significantly more resistant to levofloxacin than their respective planktonic cultures (438). Levofloxacin exposure significantly reduced biofilm viability of all strains under both medium conditions but was unable to remove completely the biofilm, and no dose-dependent antibiofilm efficacy was observed.

The timing of exposure of the biofilm to fluoroquinolone is important. Delivery of fluoroquinolones (moxifloxacin, levofloxacin, and ciprofloxacin) against early immature biofilms formed by clinical *S. maltophilia* isolates on polystyrene resulted in greater inhibition of biofilm formation than delivery against mature biofilms (439). It should be noted too that the inhibitory effects of the fluoroquinolones were not dose dependent.

Treatments of *S. maltophilia* biofilms *in vitro* with antimicrobial combinations have shown some interesting results. Erythromycin with levofloxacin treatment has resulted in altered biofilm architecture and reduced numbers of bacteria in the biofilm; erythromycin in combination with cefoperazone/sulbactam or with piperacillin also reduced biofilm colony density (400). In contrast, azithromycin has demonstrated interference with the inhibitory activity of fluoroquinolones against the biofilms (439). Polymyxins have demonstrated relatively good *in vitro* activity against Gram-negative pathogens, except for *S. maltophilia* (441). Combinations of sub-MIC polymyxin B and polysorbate 80 (0.05%) have been reported to inhibit growth and biofilm formation by *S. maltophilia* K279a and two other clinical strains, with mean growth and biofilm reductions of 89% and 98%, respectively (442). Minocycline-rifampin-impregnated central venous catheters with added chlorhexidine (CHX-M/R CVCs) have been reported to completely inhibit biofilm formation at 24 h by *S. maltophilia* 5572 and maintain antimicrobial activity after 1-year storage at 25°C (443). The outcomes of some of these studies indicate that it may be possible to bring back older antimicrobials into use.

There has been recent interest in testing the activity of plant-based compounds against *S. maltophilia* (444–447). An extracted compound (emodin) from traditional Chinese medicinal herbs significantly inhibited biofilm formation of *S. maltophilia* GIMT1.118 at 20 μM and, at 200 μM, caused almost complete cell detachment and dispersal (444). Chlorogenic acid from plant materials demonstrated a MIC range of 8 to 16 μg/ml against *S. maltophilia* and, at 1×, 2× and 4× MICs, reduced established biofilm viability of *S. maltophilia* ATCC 13637 (445). Hexane extracts (ASHE) and dichloromethane extracts (ASDE) of *Allium stipitatum* inhibited growth of *S. maltophilia* ATCC 13637, demonstrated MIC values for both of 64 μg/ml and minimal bactericidal concentration (MBC) values for both of 256 μg/ml, and exhibited bactericidal killing at 1×, 2×, and 4× MIC, eliminating >90% of *S. maltophilia* cells by 4 h of exposure (446). Against preformed *S. maltophilia* biofilms, treatment with ASHE and ASDE reduced viability in a concentration-dependent manner and disrupted biofilm structures. Celastrol, a triterpenoid compound obtained from the roots of *Tripterygium wilfordii*, exhibited MIC values of 20 μg/ml and 80 μg/ml against *S. maltophilia* strains 13637 and GNU2233, respectively, and inhibited biofilm formation without impeding planktonic growth (447). Against established biofilms, celastrol caused biofilm dispersal and reduced metabolic activity in a dose-dependent manner. At subinhibitory concentrations, celastrol inhibited *S. maltophilia* swimming motility and protease secretion

TABLE 10 Recently tested agents against *S. maltophilia* biofilm formation or established biofilms

Agent	Forming or established biofilm	Activity against biofilm	Reference
Minocycline-rifampin impregnated CVCs with added chlorhexidine	Forming	Proprietary sequential coating, complete inhibition	443
Continuous renal replacement therapy fluids (monosol S-lactate based solution, Accusol 35-bicarbonate based solution, Prismocitrate-citrated based anticoagulant, Ci-Ca K2 bicarbonate-based calcium-free dialysis fluid, 4% trisodium citrate)	Forming	Complete inhibition by Prismocitrate, Accusol 35, and trisodium citrate	435
Erythromycin in combination with levofloxacin, cefoperazone-sulbactam, or piperacillin	Forming	Decreased colony density of biofilms	400
Polymyxin in combination with polysorbate 80	Forming	Significant inhibition at sub-MIC polymyxin and 0.05% polysorbate 80	442
Extremely low-frequency magnetic field	Forming	Strain and ion species effects were noted for biomass and viability	433
Chinese herb compound Emodin	Forming	20 and 200 μM, significant inhibition	444
Clofibric acid	Forming	10× or 100× drinking water concn, no effect	165
	Established	100× drinking water concn, demonstrated reduced removal after chlorine treatment	
Celastrol	Forming	5 μg/ml inhibition by >50%	447
	Established	40 μg/ml, complete elimination and cell dispersal	
Azithromycin in combination with fluoroquinolones	Established	Significantly reduced inhibitory effect of fluoroquinolones against biofilms	439
Chlorogenic acid	Established	8 μg/ml, reduced cell viability	445
Hexane and dichloromethane extracts of *Allium stipitatum*	Established	128 μg/ml, disruption and reduction of biofilm structures	446

and repressed the transcription of *smeYZ* (of the SmeYZ efflux pump), *fsnR* (encodes the FsnR response regulator used for swimming and biofilm formation), *bfmA*, and *bfmK* (both used for biofilm formation) (447). Further research can show whether, in combination, any of these plant-derived compounds (at sub-MICs) can improve the efficacy of established antimicrobials against *S. maltophilia*.

Prevention of *S. maltophilia* biofilms on surfaces that can come into contact with humans is a major step to reducing infections by this opportunist. Cellobiose dehydrogenase (CDH) incorporation in lubricant may have potential to prevent *S. maltophilia* urinary catheter infections; a preliminary study indicates that growth of *S. maltophilia* U-57/28 was strongly inhibited in the presence of 10 mM CDH/cellobiose (448). More research is warranted to assess the efficacy of CDH against *S. maltophilia* biofilms.

The biofilm formation by *S. maltophilia* has been studied in drinking water containing chemical compounds (165, 166). Exposure of *S. maltophilia* to environmental contaminants, including nonsteroidal anti-inflammatory drugs (NSAIDs; antipyrine, diclofenac sodium salt, and ibuprofen), musk fragrances (galaxolide and tonalide), a neuroactive drug (carbamazepine), a lipid regulator (clofibric acid), and a veterinary antibiotic (tylosin), at drinking water concentrations did not significantly affect biofilm formation by *S. maltophilia* and did not alter cell viability of preformed biofilms (166). The triple combination of clofibric acid, carbamazepine, and ibuprofen at 100× drinking water concentration (100×DW) significantly reduced biofilm production, and these biofilms exhibited significantly more resistance to removal by NaOCl; in contrast, exposure to diclofenac, ibuprofen, and tylosin at 100×DW significantly increased biofilm production. Drinking water *S. maltophilia* biofilms exposed to clofibric acid at 100×DW had a significantly increased resistance to erythromycin and reduced resistance to ciprofloxacin (165). The alteration of *S. maltophilia* biofilm production and viability by environmental contaminants in drinking water is worthy of consideration during development of new water distribution systems.

A summary of recently tested agents against *S. maltophilia* biofilm formation or established biofilms is presented in Table 10.

TREATMENT OF INFECTIONS

Antimicrobials: Old and New

There remains a need to develop standardized globally accepted antimicrobial testing procedures for *S. maltophilia*. MIC determinations of antimicrobial resistance vary between countries, as they follow standards set by different agencies (e.g., Clinical and Laboratory Standards Institute, European Committee on Antimicrobial Susceptibility Testing, and the European Medicines Evaluation Agency for European Chemotherapy) (1). A recent review of treatment of invasive infections associated with *S. maltophilia* indicated that TMP-SMX was the therapy most frequently given to patients and often used in a combination therapy or as part of a sequence of antibiotics (449). Alternatives to the use of TMP-SMX for treatment of *S. maltophilia* infections have been sought. Another recent review has suggested that fluoroquinolones provide an appropriate alternative, and this has been demonstrated in a retrospective study of ventilator-associated pneumonia cases (450, 451).

Combination therapies have successfully treated *S. maltophilia* infections; a recent report indicated that a combination treatment of TMP-SMX and polymyxin-based therapy and then administration of fluoroquinolone successfully treated two patients with hematologic malignancy and *S. maltophilia* hemorrhagic pneumonia (64). A study of the use of combination therapy versus monotherapy to treat *S. maltophilia* pneumonia infections has found no difference between combination therapy and monotherapy for clinical response, development of resistance, and infection-related mortality (452). As this was a relatively small study of 458 patients, larger studies are needed to identify significant differences between these therapy approaches.

Strategies against *S. maltophilia*

Siderophore-based agents. Siderophore-based antimicrobials have been developed with good activity against *S. maltophilia* (453–471). Relatively early examples of how the active uptake of siderophores by *S. maltophilia* can be exploited to improve both the uptake and activity of antimicrobials include BAL30376 (combination of siderophore monobactam BAL19764, monobactam BAL29880 [inhibitor of class C β-lactamases], and clavulanic acid [an inhibitor of class A β-lactamases]) and the modification of lactivicin through incorporation of a catechol-type siderophore (455, 469).

Cefiderocol is a catechol siderophore cephalosporin that has received a lot of attention. This antimicrobial chelates ferric iron and uses the iron uptake system of Gram-negative bacteria to traverse the outer membrane and enter the periplasmic space, where it binds to bacterial penicillin binding protein 3 and inhibits cell wall synthesis (460, 463). Cefiderocol has demonstrated effective *in vitro* activity against multidrug-resistant *S. maltophilia*, *P. aeruginosa*, *A. baumannii*, and *Enterobacteriaceae* (453, 461). Against *S. maltophilia*, cefiderocol has exhibited a MIC_{50} range of 0.06 to 0.25 μg/ml, MIC_{90} range of 0.25 to 0.5 μg/ml, and a MIC range of $\leq$0.03 to 4 μg/ml (458–462, 464–466, 470, 471). Interestingly, in two SIDERO-WT studies, cefiderocol exhibited a higher MIC_{90} (0.5 μg/ml) against North American *S. maltophilia* isolates than against European isolates (MIC_{90} of 0.25 μg/ml) (460, 461, 466). Cefiderocol has exhibited a lower MIC_{90} value than cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, COL, piperacillin-tazobactam, and meropenem (459, 460, 462) and lower MIC value than ceftazidime, cefepime, meropenem, piperacillin-tazobactam, ceftazidime-avibactam, ceftolozane-tazobactam, COL, amikacin, and ciprofloxacin (464). In the ARGONAUT (ARLG reference group for the testing of novel therapeutics) study, cefiderocol exhibited a MIC_{90} of 0.25 mg/liter against *S. maltophilia* clinical isolates (with bla_{L1}) collected worldwide, lower than that of tigecycline (MIC_{90} of 2 mg/liter) (465). Breakpoints for cefiderocol of 4 μg/ml (susceptible), 8 μg/ml (intermediate), and 16 μg/ml (resistant) against *S. maltophilia* have been approved by CLSI (457).

The pharmacokinetic and pharmacodynamics profiles of cefiderocol have been reported (467, 468). In the murine lung infection model, the mean cumulative percentage of a 24-h period in which the free drug concentration in plasma exceeds the MIC

(%$fT_{>MIC}$) for *S. maltophilia* was 53.9% ± 18.1% (468). In the murine thigh infection model, infusion of cefiderocol using human therapeutic dose regimens resulted in >2-log killing and overall significantly higher antibacterial activity than ceftazidime (456). An international, multicenter phase 3 CREDIBLE-CR study has found that cefiderocol may be a viable therapy for patients with carbapenem-resistant Gram-negative infections (454). Resistance to siderophore-based antimicrobials is of concern. In one study, *S. maltophilia* resistance emerged to the siderophore-incorporated triple combination antimicrobial BAL30376 (468). In summary, cefiderocol shows promise against *S. maltophilia*, including multidrug-resistant strains.

Tetracyclines. From surveillance studies of the tetracycline antibiotics, tigecycline, eravacycline, and minocycline, have demonstrated efficacy against *S. maltophilia* (2, 5, 472–478). Across five surveillance studies, tigecycline exhibited a range of $MIC_{50/90}$ values of 0.5 to 2/2 to 4 μg/ml and MIC range of 0.06 to >16 μg/ml (2, 474, 475, 477, 478). In a 2011–2014 SENTRY surveillance study of 141 *S. maltophilia* isolates from Latin American medical centers, tigecycline demonstrated a $MIC_{50/90}$ of 0.5/2 μg/ml with 91.5%/83.0% inhibited at ≤2/≤1 μg/ml (477). In a global 2013–2014 SENTRY surveillance study of 372 *S. maltophilia* isolates from medical centers in Europe and the Asia-Pacific region, tigecycline demonstrated a $MIC_{50/90}$ of 0.5/2 μg/ml and a MIC range of 0.06 to 8 μg/ml (475). In a CANWARD 2014–2015 surveillance study, tigecycline exhibited a $MIC_{50/90}$ of 1/4 μg/ml with a range of 0.25 to 16 μg/ml against 118 *S. maltophilia* isolates (478). In an International Network for Optimal Resistance Monitoring (INFORM) 2015–2017 study including 309 *S. maltophilia* isolates, tigecycline exhibited a $MIC_{50/90}$ of 1/2 mg/liter, and minocycline exhibited a $MIC_{50/90}$ of 0.5/2 mg/liter with 100% susceptible isolates (CLSI) in comparison to TMP-SMX with a $MIC_{50/90}$ of ≤0.5/≤0.5 mg/liter with 95.5%/98.1% susceptible isolates (CLSI/EUCAST) (2). In a recent study of 1,210 *S. maltophilia* isolates recovered worldwide during 2013 to 2017, tigecycline demonstrated a $MIC_{50/90}$ of 2/4 μg/ml and a MIC range of 0.06 to >16 μg/ml in comparison to TMP-SMX (tested against 1,080 isolates), with a $MIC_{50/90}$ of 0.5/4 μg/ml, MIC range of <0.03 to >64 μg/ml, and 84.3% (CLSI) and 90.3% (EUCAST) susceptible isolates (474). In a small study of 48 *S. maltophilia* isolates from Brazilian hospitals, tigecycline exhibited a $MIC_{50/90}$ of 1/4 μg/ml and a MIC range of 0.25 to 16 μg/ml; in comparison, minocycline demonstrated a $MIC_{50/90}$ of 0.5/2 μg/ml with a MIC range of <0.25 to 8 μg/ml (476). Synergy has been observed *in vitro* for tigecycline-cefoperazone-sulbactam and tigecycline-levofloxacin combinations against *S. maltophilia* (479). Infection model studies are required to assess the efficacy of such combinations. In summary, tigecycline continues to be a reasonable therapeutic option for treatment of *S. maltophilia* infections.

Across four surveillance studies, minocycline has demonstrated a $MIC_{50/90}$ range of 0.5 to 2/2 to 4 μg/ml against *S. maltophilia* (2, 5, 472, 473). Minocycline exhibited the highest *in vitro* antimicrobial activity against 6,467 *S. maltophilia* clinical isolates recovered from 259 medical centers in the Asia-Pacific, Latin American, and North American regions in the 1997–2016 SENTRY surveillance study (5). Minocycline was included in the SENTRY program starting in 2005 and tested against 59.8% of the total number of *S. maltophilia* isolates. Minocycline exhibited a $MIC_{50/90}$ of ≤1/2 mg/liter with 99.5% susceptible isolates (CLSI concentration). The activity of minocycline was higher than that of TMP-SMX, which exhibited a $MIC_{50/90}$ of ≤0.5/1 mg/liter with 96.2% susceptible isolates (EUCAST concentration), and higher than that of tigecycline or levofloxacin. Minocycline exhibited *in vitro* activity with a $MIC_{50/90}$ of 1/4 mg/liter and 90% susceptible isolates against TMP-SMX-resistant *S. maltophilia* isolates that also demonstrated levofloxacin MIC values of ≥4 mg/liter. The *S. maltophilia* isolates recovered from all geographic regions showed an overall susceptibility of >99.0% to minocycline (5). In a 2014–2018 SENTRY surveillance study including 1,289 *S. maltophilia* isolates, minocycline exhibited a $MIC_{50/90}$ of 0.5/2 μg/ml with 99.5% susceptible isolates; against TMP-SMX-resistant *S. maltophilia* isolates, minocycline demonstrated activity (92.8% of the isolates were susceptible) with a $MIC_{50/90}$ of 1/4 μg/ml (473). In a 2008–2018 SENTRY

surveillance study including 41 *S. maltophilia* isolates, minocycline exhibited a $MIC_{50/90}$ of 2/4 μg/ml with a MIC range of 0.125 to 8 μg/ml with 92.7% susceptible isolates; 78.6% of the isolates that were both levofloxacin resistant and TMP-SMX resistant demonstrated susceptibility to minocycline (472). In summary, the data described above indicate that minocycline may present an alternative treatment for *S. maltophilia* isolates resistant to levofloxacin and/or TMP-SMX.

Eravacycline and tigecycline both exhibited a $MIC_{50/90}$ of 1/4 μg/ml and a MIC range of 0.25 to 16 μg/ml against 118 *S. maltophilia* isolates acquired from Canadian hospital laboratories in a CANWARD surveillance study during 2014 to 2015 (478). Against 1,210 *S. maltophilia* isolates recovered worldwide during 2013 to 2017, eravacycline demonstrated a $MIC_{50}/_{90}$ of 1/2 μg/ml and a MIC range of 0.03 to 16 μg/ml in comparison to tigecycline ($MIC_{50/90}$ of 2/4 μg/ml and MIC range of 0.06 to $>$16 μg/ml) and TMP-SMX (tested against 1,080 isolates, $MIC_{50/90}$ of 0.5/4 μg/ml, MIC range of $\leq$0.03 to $>$64 μg/ml, and 84.3% [CLSI] and 90.3% [EUCAST] susceptible isolates) (474). Eravacycline has exhibited greater activity than tigecycline across difficult-to-treat pathogens (474). Eravacycline thus provides another option for treatment of *S. maltophilia* infection.

β-Lactamase inhibitors. The β-lactamases (L1 and L2) of *S. maltophilia* continue to be a target for pharmaceutical intervention. The β-lactamase inhibitor avibactam has been reported to competitively and reversibly inhibit L2 and reestablish sensitivity of *S. maltophilia* to aztreonam (36, 480). Synergy has been observed between ceftazidime-avibactam and aztreonam, and this combination has been used to treat bacteremia due to a *S. maltophilia* strain with resistance to trimethoprim-sulfamethoxazole and other antibiotics, including ceftazidime, meropenem, levofloxacin, minocycline, and colistimethate sodium (36). In addition to avibactam, two other β-lactamase inhibitors, clavulanic acid and bicyclic boronate 2, have demonstrated reversal of aztreonam resistance in ceftazidime-susceptible *S. maltophilia*, and all of the inhibitors reversed ceftazidime and aztreonam resistance in a ceftazidime-resistant hyperproducing β-lactamase *S. maltophilia* mutant (481). Against *S. maltophilia* from chronically infected adult patients, aztreonam-avibactam demonstrated an MIC range of 1 to 32 μg/ml with a $MIC_{50/90}$ of 8/16 μg/ml in comparison to aztreonam alone (MIC range of $>$128 μg/ml and $MIC_{50/90}$ of $>$128 μg/ml), suggesting that aztreonam-avibactam may be a viable treatment against *S. maltophilia* infection (482).

In a SENTRY surveillance study, a different β-lactamase inhibitor, vaborbactam, when used in combination with meropenem against *S. maltophilia*, exhibited a $MIC_{50/90}$ of $>$32/>32 μg/ml, indicating that the combination exhibited limited efficacy against this pathogen (483).

Improved antimicrobial activity of a cephalosporin through combination with other β-lactamase inhibitors is possible. Against bloodstream *S. maltophilia* isolates, ceftolozane-tazobactam demonstrated greater activity than ceftazidime alone (484), and cefepime-tazobactam exhibited lower MIC values than cefepime alone against *S. maltophilia* clinical isolates (485). Ceftolozane-tazobactam has demonstrated reasonable activity against *S. maltophilia* from CF adult patients, with a $MIC_{50/90}$ of $>$256/1.5 μg/ml; no clinical breakpoint has been established, but with using a selected value of $\leq$4 μg/ml, approximately 60% of *S. maltophilia* isolates were susceptible to this combination treatment (486). In another study, ceftolozane-tazobactam exhibited a MIC_{90} of 8 μg/ml against *S. maltophilia* from CF respiratory samples (487).

In a small study, *S. maltophilia* isolates that exhibited resistance to β-lactams (aztreonam), fluoroquinolones, colistin, and TMP-SMX demonstrated susceptibility to the combinations of aztreonam with ceftazidime-avibactam, ceftolozane-tazobactam, or amoxicillin-clavulanate; aztreonam in combination with amoxicillin-clavulanate has been used to successfully treat a 60-year-old patient with decompensated chronic obstructive pulmonary disease (488).

Few studies have examined the activity of the combination ceftazidime-avibactam (489–491). Ceftazidime-avibactam did not show improved activity compared to that of ceftazidime alone against 34 *S. maltophilia* isolates recovered from CF patient

respiratory samples ($MIC_{50/90}$ of 140/256 mg/liter with 35% susceptible isolates) (489). Similar findings were observed when ceftazidime, ceftazidime-avibactam, ceftolozane-tazobactam, meropenem, meropenem-vaborbactam, and piperacillin-tazobactam were tested against 100 *S. maltophilia* CF isolates; none of the β-lactam–β-lactamase inhibitor combinations demonstrated improved activity compared to that of their respective β-lactam counterpart (490). In a third study of 54 clinical *S. maltophilia* isolates recovered in one hospital, ceftazidime-avibactam demonstrated a MIC of $<1\ \mu g/ml$ with 30% susceptible isolates compared to only 2% of the isolates with this MIC for ceftazidime alone. The MIC_{50} values for ceftazidime-avibactam and ceftazidime were 2 and 12 μg/ml. The proportion of susceptible isolates for ceftazidime-avibactam was 66.7% in comparison to 38.9% of the isolates demonstrating susceptibility to ceftazidime alone (491). The disparity between these studies may reflect possible clonally related isolates used in the latter study. In summary, these studies indicate that β-lactamase inhibitors may be able to reverse resistance to some antimicrobials, but their use in combination therapies is limited, as only select antimicrobials have shown improved activity when combined with a β-lactamase inhibitor.

Antimicrobial peptides. Several antimicrobial peptides have been assessed for their activity against *S. maltophilia* and its biofilms (492–499). Esculentin-2CHa and its analogs have been tested for their activity against clinical meropenem-resistant *S. maltophilia*; the analogs (D20K and D27K) exhibited the lowest MIC values (1.5 to 3 μM) against *S. maltophilia* strains but demonstrated significant hemolytic activity (492). Pseudhymenochirin-1Pb and pseudhymenochirin-2Pa that exhibited lethal activity against adenocarcinomas and *S. maltophilia* clinical isolates also demonstrated hemolytic activity (493). For use in treatment of cancer or bacterial infections, further modifications of these peptides are required to eliminate cytotoxicity toward erythrocytes. In comparison, the dimer peptide LfcinB $(20\text{-}25)_2$, derived from bovine lactoferrin, has exhibited a MIC of 50 μg/ml against *S. maltophilia* ATCC 13636 and has no hemolytic activity (494). Future studies will determine the efficacy of LfcinB $(20\text{-}25)_2$ against *S. maltophilia* biofilms *in vitro* and *in vivo*.

Cathelicidin-derived peptides SMAP-29, BMAP-27, and BMAP-28 at sublethal concentrations significantly inhibited biofilm formation, exhibited dose-dependent effects against established clinical *S. maltophilia* biofilms, and demonstrated some strain-specific effects (495). BMAP-27, BMAP-28, and artificial peptide P19(9/B) demonstrated strain-specific bactericidal activity against *S. maltophilia* and significantly inhibited biofilm formation of *S. maltophilia* when tested at subinhibitory concentrations; however, they were not as effective at inhibition as tobramycin (496). A study of shortened BMAPs reported that BMAP-27(1-18) demonstrated the lowest toxicity in C57BL/6NCrl mice and exhibited various degrees of bactericidal and antibiofilm activity against CF patient *S. maltophilia* strains (497). Combinations of peptides with antimicrobials have been tested. Peptide LL37 and the macrolide azithromycin have exhibited synergy against *S. maltophilia* K279a cells cultured in tissue culture medium (RPMI plus 10% LB) (498). Against clinical *S. maltophilia*, LL37 has exhibited MIC values of 3.3 to 34.6 mg/liter; at the lower range of the MIC, this was comparable to that of ciprofloxacin (499). In summary, use of antimicrobials in combination with antimicrobial peptides may hold some promise for use in treatment of *S. maltophilia* biofilms, providing the peptide does not present adverse effects to the infected host.

Cell envelope targets. The outer membrane of *S. maltophilia* serves as a barrier of protection against antimicrobials. The multidrug-resistant efflux pumps have been considered targets for lowering the MIC values for antimicrobials used to treat *S. maltophilia* infections. For example, the efflux pump inhibitor elacridar has exerted a dose-dependent decrease on the MIC for ciprofloxacin against *S. maltophilia* (500). As this study tested one *S. maltophilia* strain, it would be useful to determine if elacridar treatment results in strain-specific effects when more *S. maltophilia* strains are tested. Exposure to COL increased the outer membrane permeability and reduced the MIC of MD3, a type I signal peptidase inhibitor, against clinical and environmental

S. maltophilia isolates (501). Further research is needed to identify additional peptidase inhibitors that may be useful against *S. maltophilia* if used in combination with membrane-permeabilizing agents. *S. maltophilia* demonstrates susceptibility to argyrin B, a natural cyclic peptide inhibitor of bacterial elongation factor G; the susceptibility of *E. coli* to argyrin B is reduced when efflux pumps are nonfunctional (502). It will be interesting to see if the efflux pumps of *S. maltophilia* also play a role in determining resistance to argyrin B. In addition to the inhibitors described above, a recent study has reported inhibitors of the cell division protein FtsZ have activity against *S. aureus* (503). It remains to be seen whether effective anti-FtsZ agents can be generated against *S. maltophilia*.

Silver. Silver has long been recognized for its antimicrobial activity. In a small study that assessed the efficacy of silver alginate (SA) and silver carboxymethylcelluose (SCMC) dressings against multidrug-resistant *S. maltophilia* recovered from burn patients, both dressings were significantly more effective at pH 5.5 than at pH 8.5, and the SCMC dressing was significantly more effective than the SA dressing at pH 8.5 (504). Silver nanoparticles have demonstrated activity against *S. maltophilia* (505–507). Silver nanoparticles are known to disrupt outer membrane integrity via the production of reactive oxygen species (508), and they are active against *S. maltophilia* planktonic cells and biofilms. Radiosterilized pig skin-silver nanocomposites impregnated with different suspension concentrations (ppm) of silver nanoparticles inhibited *S. maltophilia* (recovered from burn patients) growth in a dose-dependent manner and inhibited biofilm formation, and no viable bacteria were recovered from disaggregated biofilms exposed to nanocomposites impregnated with a silver suspension of 250 ppm (505). At this concentration of silver, exposure of adipose-derived mesenchymal stem cells resulted in a cell viability of ≥80% and positive cell culture; against these cells, the nanocomposites exhibited dose-dependent cytotoxicity (505). In another study against CF respiratory *S. maltophilia* strains, the MIC of silver nanoparticles (AgNPs) was 4.25 μg/ml, and the killing of bacteria by the AgNPs was time and concentration dependent (506). At 4× MIC, the AgNPs were able to reduce preformed biofilm viability of the strongest biofilm-producing strain tested. At the concentrations tested, the AgNPs did not demonstrate toxicity against *G. mellonella* larvae. In a small study, synergy has been reported for the combination of polymyxin B and silver nanoparticles against a polymyxin B-resistant *S. maltophilia* clinical isolate *in vitro*, and synergy was also seen at clinically relevant concentrations against polymyxin-resistant *P. aeruginosa*, *A. baumannii*, and *Klebsiella pneumoniae* (507). Quaternary ammonium polyethyleneimine nanoparticles have demonstrated a MIC of 12.5 μg/ml and inhibited growth of a clinical drug-resistant *S. maltophilia* isolate; the MIC was well below the cytotoxic concentration of 100 μg/ml for the human cell line HEK293T (509). Larger-scale studies with these nanoparticles against more *S. maltophilia* strains recovered from different infections should provide information about any strain-dependent effects. In summary, to consider therapeutic applications for these nanoparticles and nanocomposites, research is needed to test the efficacy of them *in vivo*.

***N*-Acetylcysteine.** The mucolytic agent *N*-acetylcysteine has demonstrated activity against *S. maltophilia* planktonic cells and established biofilms (510, 511). *N*-Acetylcysteine exhibited a range of MICs of 16 to 32 μg/ml, and a dose-dependent, time-dependent, and strain-dependent antibiofilm effect of *N*-acetylcysteine was observed against *S. maltophilia* (510). Against established biofilms of some strains, *N*-acetylcysteine reduced the cell viability by at least 4 log CFU/peg (510). Synergy has been observed *in vitro* for COL and *N*-acetylcysteine against *S. maltophilia* planktonic cells and biofilms (511). Against planktonic cells, a dose-dependent enhancement of colistin activity by *N*-acetylcysteine was observed, and against most COL-resistant preformed *S. maltophilia* biofilms, this combination demonstrated synergy. *N*-Acetylcysteine enhanced COL antibiofilm activity in a dose-dependent manner (511). It will be interesting to see the efficacy of *N*-acetylcysteine *in vivo* and to determine whether its combination with other membrane-permeabilizing agents such as polymyxin B also results in synergy.

Plant compounds. Plant compounds have demonstrated antimicrobial activities against *S. maltophilia* (512, 513). Against CF *S. maltophilia* isolates *in vitro*, green tea compound epigallocatechin-3-gallate (EGCg) exhibited a MIC range of 64 to 512 mg/liter. C57BL/6 mice and *Cftr* mutant mice were treated with EGCg (1,024 mg/liter) and challenged with *S. maltophilia*. EGCg-treated mice had significantly reduced *S. maltophilia* counts compared to mice treated with COL. EGCg protected *Cftr* mutant mice against pulmonary *S. maltophilia* infection. Against young and established biofilms, EGCg displayed strain-dependent effects, and a lack of dose dependency was observed for the viability of mature biofilms (512). Cinnamic acid, phloretin, ferulic acid, *p*-coumaric acid, caffeic acid, (−)-epigallocatechin, and (−)-gallocatechin have demonstrated inhibitory action against *S. maltophilia*; cinnamic acid exhibited the lowest MIC (0.125 mg/ml) and damaged the bacterial cell membrane integrity (513). To the author's knowledge, these plant compounds have not been used against *S. maltophilia* infection in humans. Research is needed to see if these compounds can improve the activity of older antimicrobials without adverse effects on the host.

Preliminary studies. Three new antimicrobial agents have demonstrated activity against *S. maltophilia* (514–516). A novel membrane-active agent with aromatic linker, compound 2n, exhibited a MIC value of 1 μg/ml against *S. maltophilia*, with low toxicity (514). POL7306, a peptidomimetic antibiotic, exhibited a $MIC_{50/90}$ of 0.06/0.25 mg/liter against 51 *S. maltophilia* isolates in a 2017–2018 SENTRY survey in comparison to TMP-SMX and levofloxacin, with $MIC_{50/90}$ values of $\leq$0.5/$\leq$0.5 mg/liter and 1/4 mg/liter, respectively (515). POL7306 acts by binding to an outer membrane protein (517). Glucocorticoid PYED-1 (pregnadiene-11-hydroxy-16α,17α-epoxy-3,20-dione-1), a synthetic precursor of deflazacort, demonstrated a MIC range of 64 to 512 μg/ml against clinical *S. maltophilia* isolates and significantly inhibited biofilm formation at subinhibitory concentrations, and synergy was noted for PYED-1 when combined with gentamicin and amikacin (516). As each of these compounds has been identified recently, more research is needed to look at the activity of these compounds across *S. maltophilia* strains of different origins, examine their effects on host cells, and determine their pharmacokinetics.

In summary, there has been much creative thought given to the development of new anti-infective strategies against this pathogen. Given the extensive array of drug resistance determinants possessed by *S. maltophilia*, it is likely that novel combinations of antimicrobials and not single antimicrobial agents will provide an effective measure to impede infection by, if not eliminate, this opportunist.

S. MALTOPHILIA AND BIOTECHNOLOGY

S. maltophilia is an environmental bacterium of keen interest in biotechnology due to its ability to produce inhibitory molecules, nanoparticles, and enzymes useful for applications, including anti-infection, food production, agriculture, and protection of the environment. Some recent examples are described below.

Antimicrobial Activity against Clinically Relevant Pathogens

Environmental *S. maltophilia* strains have exhibited antimicrobial activity against bacteria and fungi (518–523). *S. maltophilia* strain BJ01 secretes *cis*-9-octadecenoic acid that exhibited quorum-quenching activity and inhibited biofilms by *P. aeruginosa* ATCC 9027 (518). *S. maltophilia* recovered from the shrub *Fagonia indica* has demonstrated inhibitory activity against *K. pneumoniae* ATCC 4649, *Bacillus subtilis* ATCC 6633, *Mucor mycosis* FCPB 0041, *Aspergillus flavus* FCPB 0064, *A. fumigatus* FCPB 1264, *Aspergillus niger* FCBP 0198, and promastigotes of *Leishmania tropica* and cytotoxicity toward *Streptomyces* 85E (519).

S. maltophilia strains have demonstrated antimicrobial activity against major clinical pathogens, including *K. pneumoniae*, *P. aeruginosa*, and *S. aureus* (520, 521). A selenite-reducing *S. maltophilia* SelTE02 strain isolated from the roots of *Astragalus bisulcatus* (520) produced selenium nanoparticles that demonstrated nanoparticle size-dependent antimicrobial activity, with MIC values of 125 mg/liter for *E. coli* JM109 and *E. coli*

ATCC 25922 and 250 mg/liter for *P. aeruginosa* PAO1, *P. aeruginosa* ATCC 27853, and *S. aureus* ATCC 25923 (521). *S. maltophilia* SeITE02 selenium nanoparticles have demonstrated MIC values in the clinical usage range (8 and 16 μg/ml) against 4 of 7 *P. aeruginosa* clinical strains (522). At a concentration of $\geq$100 μg/ml, these nanoparticles inhibited biofilm synthesis as high as 96% $\pm$ 1.5% by tested *P. aeruginosa* strains and, with tested *Candida* strains, inhibited biofilm synthesis 60% to 70% at a nanoparticle concentration of 50 μg/ml (>92% inhibition at 500 μg/ml). At the highest tested dose (500 μg/ml), the nanoparticles did not induce apoptosis of, induce cytokine release from, or stimulate the production of reactive oxygen species in isolated human dendritic cells or human primary fibroblast CCD1112Sk cells (522). Denaturation of these nanoparticles following treatment with SDS and elevated temperature reduces their antimicrobial and antibiofilm activity and results in increased MIC values for *P. aeruginosa*, *S. maltophilia*, *Achromobacter xylosoxidans*, *B. cenocepacia*, *S. aureus*, *Staphylococcus haemolyticus*, and *Staphylococcus epidermidis* (523). As these nanoparticles show promise for treatment of infections *in vivo*, work is needed to fully elucidate the mode of action of these nanoparticles. It would be interesting to use a model of infection and determine whether host cell components interfere with the activities of the nanoparticles.

Antimicrobial activity of *S. maltophilia* can also be observed against different strains of *S. maltophilia*. The bacteriocin maltocin P28, produced by *S. maltophilia* strain P28, exhibits bactericidal activity against some *S. maltophilia* strains (524). Endolysin P28 (encoded within the maltocin P28 gene cluster) produced by *S. maltophilia* exhibits lytic activity against genera that include *Pseudomonas*, *Staphylococcus*, *Escherichia*, *Bacillus*, *Klebsiella*, *Xanthomonas*, *Proteus*, *Salmonella*, *Listeria*, *Shigella*, and *Aeromonas* and demonstrates hydrolysis of peptidoglycan (525).

Biocontrol and Bioremediation

Additional insights about *S. maltophilia* can be seen in the areas of biocontrol and bioremediation. Recent studies have investigated the use of environmental *S. maltophilia* strains in such applications (199, 526–534).

In a study to investigate its potential as a biocontrol agent, endophyte isolate *S. maltophilia* CR71 culture supernatant demonstrated weak antifungal activity against gray mold phytopathogen *Botrytis cinerea* (526). On the other hand, *S. maltophilia* has impeded another biocontrol agent (199). *S. maltophilia* recovered from the mucus and macerate of *Stomoxys calcitrans* (stable fly) larvae has exhibited growth inhibition of *Beauveria bassiana sensu lato* isolates CG 138, CG 228, and ESALQ 986 and subsequently hindered the use of this fungus for biocontrol of the parasitic *S. calcitrans* (199). It is not clear which component of *S. maltophilia* is responsible for these antifungal activities. The proteolytic activity of *S. maltophilia* (PD 4560) has demonstrated biocontrol of *Ralstonia* potato wilt disease through its antibacterial activity against the soil-associated pathogen *Ralstonia solanacearum in vitro* and *in vivo* (527). An extracellular protease of rhizosphere *S. maltophilia* N4 has exhibited biocidal activity toward the nematodes, *C. elegans* and *Panagrellus* spp. (528).

Studies have identified *S. maltophilia* strains that are capable of degrading and transforming antimicrobials and environmental contaminants that may be released into the environment as wastes (529–532). *S. maltophilia* ZJB-14120 has been reported to degrade abamectin (an antiparasitic and acaricide), emamectin, erythromycin, and spiramycin, indicating a potential application for its use in the treatment of contaminated soils and water (529). *S. maltophilia* has been reported to degrade carbendazim (a fungicide) in polluted water, and the bacterium's degradation kinetics have been reported (530, 531). *S. maltophilia* strain DT1 has been reported to transform tetracycline (532). *S. maltophilia* strains SJTH1 and SJTL3 have demonstrated the ability to degrade estrogen in various environments (533, 534).

Agriculture

The rhizospheric *S. maltophilia* strains have contributed to agriculture through their association with plants. *S. maltophilia* is recognized as a plant endosymbiont (535, 536).

Promotion of seed germination and plant growth by *S. maltophilia* R551-3 has been reported for oilseed rape plants, and the *rpf*/DSF system contributes to the bacterium's colonization of the plant (419). In a recent study, *S. maltophilia* SPB-9 was observed to improve the growth of wheat plants, provided them with protection against salinity stress, and increased their immune defenses against challenge with a fungal pathogen (537). Halotolerant *S. maltophilia* BJ01 promoted growth of peanut plants under salinity stress and nitrogen limiting conditions (538, 539). In summary, these studies demonstrate the beneficial qualities of environmental *S. maltophilia* strains for agricultural crops.

FUTURE CHALLENGES

Continued surveillance and monitoring of the resistance of *S. maltophilia* to antimicrobials is warranted. Due to the observed increase in antibiotic resistance of *S. maltophilia* over the decades, new strategies will need to be developed against this opportunistic pathogen. Several strategies have been discussed in this review, and there are still others that remain to be explored.

Research has focused on gaining a more thorough understanding of the resistance mechanisms used by *S. maltophilia* against antimicrobials. The interplay of genetic mechanisms between the various strategies used by *S. maltophilia* in its defense against antimicrobials and its ability to survive, colonize, form biofilms, and persist needs to continue to be elucidated.

S. maltophilia has, at its disposal, a wide array of properties to deploy during colonization and infection. Advances are being made in our knowledge of the virulence factors used by this pathogen. Further work is needed in the area of host-pathogen interactions to identify suitable strategies for prevention and treatment of *S. maltophilia* infection.

The antimicrobial resistance of the biofilms of *S. maltophilia* is a significant feature of this human opportunist. These biofilms are sensitive to nutrient conditions and other environmental factors. Climate change may well alter how this pathogen colonizes, survives, and forms biofilms within susceptible individuals and on abiotic surfaces. The work under way to examine genetic heterogeneity among strains of *S. maltophilia* is of particular interest as genogroups and lineages are characterized, raising the possibility of antibiotic resistance reservoirs, in particular, host populations, and posing questions about the possible adaptation of strains to their habitat.

Progress is being made toward our understanding of the differences in infections by *S. maltophilia* alone and *S. maltophilia*-associated polymicrobial infections. It is important to develop standardized globally accepted protocols for antimicrobial susceptibility testing of *S. maltophilia* biofilms. For the development of appropriate pharmaceutical interventions/treatments, work needs to continue toward a better understanding of the interactions between *S. maltophilia* and other microbes in biofilms, during different types of infection, and subsequently with the susceptible host.

In the clinical setting, the maintenance of good hygiene practices such as handwashing, use of sterilized water, and the deliberate measured appropriate use of antibiotics are steps toward reducing the risk of *S. maltophilia* infection. In both the community and clinical environment, the monitoring of the water distribution systems and appropriate disinfection of contaminated hardware and devices that come into contact with humans can also help reduce transmission of *S. maltophilia* to susceptible individuals.

S. maltophilia is an environmental biofilm-forming microbe and often multidrug resistant. As mentioned earlier, biofilms can serve as niches for antimicrobial resistance gene transfer between cells. It is reasonable that this drug resistance is maintained by the *S. maltophilia* strains on entry into the susceptible debilitated host and, subsequently, the clinical setting. Currently, *S. maltophilia* infection of healthy individuals remains infrequent.

In addition to its activities as an opportunistic pathogen, *S. maltophilia* has several beneficial qualities that include as a plant endosymbiont to enhance plant growth, its

secretion of compounds that inhibit other pathogens, and its degradation of antimicrobials and contaminants released into soils and water in the environment. The challenge is to control its ability to come in contact with, infect, and cause disease in humans and other organisms.

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REFERENCES

1. Brooke JS. 2012. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. Clin Microbiol Rev 25:2–41. https://doi.org/10.1128/CMR.00019-11.
2. Sader HS, Castanheira M, Mendes RE, Flamm RK. 2018. Frequency and antimicrobial susceptibility of Gram-negative bacteria isolated from patients with pneumonia hospitalized in ICUs of US medical centres (2015–17). J Antimicrob Chemother 73:3053–3059. https://doi.org/10.1093/jac/dky279.
3. Gales AC, Castanheira M, Jones RN, Sader HS. 2012. Antimicrobial resistance among Gram-negative bacilli isolated from Latin America: results from SENTRY Antimicrobial Surveillance Program (Latin America, 2008–2010). Diagn Microbiol Infect Dis 73:354–360. https://doi.org/10.1016/j.diagmicrobio.2012.04.007.
4. Sader HS, Farrell DJ, Flamm RK, Jones RN. 2014. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009–2012. Int J Antimicrob Agents 43:328–334. https://doi.org/10.1016/j.ijantimicag.2014.01.007.
5. Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. 2019. Antimicrobial susceptibility of *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex and *Stenotrophomonas maltophilia* clinical isolates: results from the SENTRY Antimicrobial Surveillance Program (1997–2016). Open Forum Infect Dis 6:S34–S46. https://doi.org/10.1093/ofid/ofy293.
6. Liu YM, Chen YS, Toh HS, Huang CC, Lee YL, Ho CM, Lu PL, Ko WC, Chen YH, Wang JH, Tang HJ, Yu KW, Liu YC, Chuang YC, Xu Y, Ni Y, Liu CE, Hsueh PR. 2012. *In vitro* susceptibilities of non-*Enterobacteriaceae* isolates from patients with intra-abdominal infections in the Asia-Pacific region from 2003 to 2010: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). Int J Antimicrob Agents 40:S11–S17. https://doi.org/10.1016/S0924-8579(12)70004-3.
7. Brooke JS. 2014. New strategies against *Stenotrophomonas maltophilia*: a serious worldwide intrinsically drug-resistant opportunistic pathogen. Expert Rev Anti Infect Ther 12:1–4. https://doi.org/10.1586/14787210.2014.864553.
8. Jang TN, Wang FD, Wang LS, Liu CY, Liu IM. 1992. *Xanthomonas maltophilia* bacteremia: an analysis of 32 cases. J Formos Med Assoc 91:1170–1176.
9. Victor MA, Arpi M, Bruun B, Jønsson V, Hansen MM. 1994. *Xanthomonas maltophilia* bacteremia in immunocompromised hematological patients. Scand J Infect Dis 26:163–170. https://doi.org/10.3109/00365549409011780.
10. Denton M, Kerr KG. 1998. Microbiological and clinical aspects of infection associated with *Stenotrophomonas maltophilia*. Clin Microbiol Rev 11:57–80. https://doi.org/10.1128/CMR.11.1.57.
11. Hugh R, Leifson E. 1963. A description of the type strain of *Pseudomonas maltophilia*. Int J Syst Evol Microbiol 13:133–138. https://doi.org/10.1099/0096266X-13-3-133.
12. Maes M. 1993. Fast classification of plant-associated bacteria in the *Xanthomonas* genus. FEMS Microbiol Lett 113:161–165. https://doi.org/10.1111/j.1574-6968.1993.tb06508.x.
13. Nesme X, Vaneechoutte M, Orso S, Hoste B, Swings J. 1995. Diversity and genetic relatedness with genera *Xanthomonas* and *Stenotrophomonas* using restriction endonuclease site differences of PCR-amplified 16S rRNA gene. Syst Appl Microbiol 18:127–135. https://doi.org/10.1016/S0723-2020(11)80460-1.
14. Palleroni NJ, Bradbury JF. 1993. *Stenotrophomonas*, a new bacterial genus for *Xanthomonas maltophilia* (Hugh 1980) Swings et al. 1983. Int J Syst Bacteriol 43:606–609. https://doi.org/10.1099/00207713-43-3-606.
15. Palleroni NJ, Kunisawa R, Contopoulou R, Doudoroff M. 1973. Nucleic acid homologies in the genus *Pseudomonas*. Int J Syst Bacteriol 23:333–339. https://doi.org/10.1099/00207713-23-4-333.
16. Swings J, De Vos P, Van den Mooter M, De Ley J. 1983. Transfer of *Pseudomonas maltophilia* Hugh 1981 to the genus *Xanthomonas* as *Xanthomonas maltophilia* (Hugh 1981) comb. nov. Int J Syst Bacteriol 33:409–413. https://doi.org/10.1099/00207713-33-2-409.
17. Carmody LA, Spilker T, LiPuma JJ. 2011. Reassessment of *Stenotrophomonas maltophilia* phenotype. J Clin Microbiol 49:1101–1103. https://doi.org/10.1128/JCM.02204-10.
18. Gao S, Zhang Z, Zhou H, Zhu H, Shen H, Zhou W. 2019. Complete genome sequence of oxidase-positive *Stenotrophomonas maltophilia* strain SM7059. Microbiol Resour Announc 8:e01576-18. https://doi.org/10.1128/MRA.01576-18.
19. An SQ, Berg G. 2018. *Stenotrophomonas maltophilia*. Trends Microbiol 26:637–638. https://doi.org/10.1016/j.tim.2018.04.006.
20. Arthur C, Tang X, Romero JR, Gossett JG, Harik N, Prodhan P. 2015. *Stenotrophomonas maltophilia* infection among young children in a cardiac intensive care unit: a single institution experience. Pediatr Cardiol 36:509–515. https://doi.org/10.1007/s00246-014-1041-0.
21. Bao H, Qiao Y, Liu D, Chen J, Wu X, Hu X, Ma X, Wu D. 2020. The clinical impact of *Stenotrophomonas maltophilia* bacteremia on the 30-day mortality rate in patients with hematologic disorders: a single-institution experience. Infection 48:205–212. https://doi.org/10.1007/s15010-019-01369-4.
22. Batra P, Mathur P, Misra MC. 2017. Clinical characteristics and prognostic factors of patients with *Stenotrophomonas maltophilia* infections. J Lab Physicians 9:132–135. https://doi.org/10.4103/0974-2727.199639.
23. Chen Y, Suo J, Du M, Chen L, Liu Y, Wang L, Liang Z. 2019. Clinical features, outcomes, and risk factors of bloodstream infections due to *Stenotrophomonas maltophilia* in a tertiary-care hospital of China: a retrospective analysis. Biomed Res Int 2019:4931501. https://doi.org/10.1155/2019/4931501.
24. Furuichi M, Ito K, Miyairi I. 2016. Characteristics of *Stenotrophomonas maltophilia* bacteremia in children. Pediatr Int 58:113–118. https://doi.org/10.1111/ped.12745.
25. Hagiya H, Ogawa H, Ishida T, Terasaka T, Kimura K, Waseda K, Hanayama Y, Horita M, Shimamura Y, Kondo E, Otsuka F. 2014. Recurrent *Stenotrophomonas maltophilia* bacteremia after iliac crest bone graft harvest. Intern Med 53:1693–1698. https://doi.org/10.2169/internalmedicine.53.1995.
26. Hamdi AM, Fida M, Abu SO, Beam E. 2020. *Stenotrophomonas* bacteremia antibiotic susceptibility and prognostic determinants: Mayo Clinic 10-year experience. Open Forum Infect Dis 7:ofaa008. https://doi.org/10.1093/ofid/ofaa008.
27. Hashimoto T, Komiya K, Fujita N, Usagawa Y, Yamasue M, Umeki K, Ando M, Nureki S-I, Hiramatsu K, Kadota J-I. 2020. Risk factors for 30-day mortality among patients with *Stenotrophomonas maltophilia* bacteraemia. Infect Dis (Lond) 52:440–442. https://doi.org/10.1080/23744235.2020.1734653.
28. Herrera-Heredia SA, Pezina-Cantú C, Garza-González E, Bocanegra-Ibarias P, Mendoza-Olazarán S, Morfín-Otero R, Camacho-Ortiz A, Villarreal-Treviño L, Rodríguez-Noriega E, Paláu-Davila L, Maldonado-Garza HJ, Flores-Treviño S. 2017. Risk factors and molecular mechanisms associated with

trimethoprim-sulfamethoxazole resistance in *Stenotrophomonas maltophilia* in Mexico. J Med Microbiol 66:1102–1109. https://doi.org/10.1099/jmm.0.000550.

29. Hotta G, Matsumura Y, Kato K, Nakano S, Yunoki T, Yamamoto M, Nagao M, Ito Y, Takakura S, Ichiyama S. 2014. Risk factors and outcomes of *Stenotrophomonas maltophilia* bacteraemia: a comparison with bacteraemia caused by *Pseudomonas aeruginosa* and *Acinetobacter* species. PLoS One 9:e112208. https://doi.org/10.1371/journal.pone.0112208.
30. Imoto W, Yamada K, Yamairi K, Shibata W, Namikawa H, Yukawa S, Yoshii N, Nakaie K, Hirose A, Koh H, Watanabe T, Asai K, Nakamae H, Kaneko Y, Kawaguchi T, Hino M, Kakeya H. 2020. Clinical characteristics of rapidly progressive fatal hemorrhagic pneumonia caused by *Stenotrophomonas maltophilia*. Intern Med 59:193–198. https://doi.org/10.2169/internalmedicine.3358-19.
31. Kim EJ, Kim YC, Ahn JY, Jeong SJ, Ku NS, Choi JY, Yeom J-S, Song YG. 2019. Risk factors for mortality in patients with *Stenotrophomonas maltophilia* bacteremia and clinical impact of quinolone-resistant strains. BMC Infect Dis 19:754. https://doi.org/10.1186/s12879-019-4394-4.
32. Kim S-H, Cha MK, Kang C-I, Ko J-H, Huh K, Cho SY, Chung DR, Peck KR. 2019. Pathogenic significance of hemorrhagic pneumonia in hematologic malignancy patients with *Stenotrophomonas maltophilia* bacteremia: clinical and microbiological analysis. Eur J Clin Microbiol Infect Dis 38:285–295. https://doi.org/10.1007/s10096-018-3425-1.
33. Kim S-H, Cho SY, Kang C-I, Seok H, Huh K, Ha YE, Chung DR, Lee NY, Peck KR, Song J-H. 2018. Clinical predictors of *Stenotrophomonas maltophilia* bacteremia in adult patients with hematologic malignancy. Ann Hematol 97:343–350. https://doi.org/10.1007/s00277-017-3178-4.
34. Kuo S-H, Lin W-R, Lin J-Y, Huang C-H, Jao Y-T, Yang P-W, Tsai J-R, Wang W-H, Chen Y-H, Hung C-T, Lu P-L. 2018. The epidemiology, antibiograms and predictors of mortality among critically-ill patients with central line-associated bloodstream infections. J Microbiol Immunol Infect 51:401–410. https://doi.org/10.1016/j.jmii.2017.08.016.
35. Lin Y, Wang B-X, Zhang N-N, Zhang L, Gao Z-B, Tian J, Jiang X. 2019. Metagenomic analysis identified *Stenotrophomonas maltophilia* pneumonia in an infant suffering from unexplained very severe pneumonia. Front Pediatr 7:380. https://doi.org/10.3389/fped.2019.00380.
36. Mojica MF, Ouellette CP, Leber A, Becknell MB, Ardura MI, Perez F, Shimamura M, Bonomo RA, Aitken SL, Shelburne SA. 2016. Successful treatment of bloodstream infection due to metallo-β-lactamase-producing *Stenotrophomonas maltophilia* in a renal transplant patient. Antimicrob Agents Chemother 60:5130–5134. https://doi.org/10.1128/AAC.00264-16.
37. Motamedifar M, Heidari H, Yasemi M, Sedigh Ebrahim-Saraie H. 2017. Molecular epidemiology and characteristics of 16 cases with *Stenotrophomonas maltophilia* bacteraemia in pediatric intensive care units. Ann Ig 29:264–272. https://doi.org/10.7416/ai.2017.2154.
38. Mutlu M, Yılmaz G, Aslan Y, Bayramoğlu G. 2011. Risk factors and clinical characteristics of *Stenotrophomonas maltophilia* infections in neonates. J Microbiol Immunol Infect 44:467–472. https://doi.org/10.1016/j.jmii.2011.04.014.
39. Osawa K, Shigemura K, Kitagawa K, Tokimatsu I, Fujisawa M. 2018. Risk factors for death from *Stenotrophomonas maltophilia* bacteremia. J Infect Chemother 24:632–636. https://doi.org/10.1016/j.jiac.2018.03.011.
40. Samonis G, Karageorgopoulos DE, Maraki S, Levis P, Dimopoulou D, Spernovasilis NA, Kofteridis DP, Falagas ME. 2012. *Stenotrophomonas maltophilia* infections in a general hospital: patient characteristics, antimicrobial susceptibility, and treatment outcome. PLoS One 7:e37375. https://doi.org/10.1371/journal.pone.0037375.
41. Tian L, Sun Z, Zhang Z. 2018. Antimicrobial resistance of pathogens causing nosocomial bloodstream infection in Hubei Province, China, from 2014 to 2016: a multicenter retrospective study. BMC Public Health 18:1121. https://doi.org/10.1186/s12889-018-6013-5.
42. Tokatly Latzer I, Nahum E, Cavari Y, Lazar I, Ben-Ari Y, Ben-Shimol S, Ben-Shalom G, Geffen Y, Goldberg L, Rubinstein M, Keller N, Pessach IM, Paret G. 2019. Treatment outcomes of *Stenotrophomonas maltophilia* bacteremia in critically ill children: a multicenter experience. Pediatr Crit Care Med 20:e231–e239. https://doi.org/10.1097/PCC.0000000000001919.
43. Wang C-H, Lin J-C, Chang F-Y, Yu C-M, Lin W-S, Yeh K-M. 2017. Risk factors for hospital acquisition of trimethoprim-sulfamethoxazole resistant *Stenotrophomonas maltophilia* in adults: a matched case-control study. J Microbiol Immunol Infect 50:646–652. https://doi.org/10.1016/j.jmii.2016.12.007.
44. Wang CH, Yu C-M, Hsu S-T, Wu R-X. 2020. Levofloxacin-resistant *Stenotrophomonas maltophilia*: risk factors and antibiotic susceptibility patterns in hospitalized patients. J Hosp Infect 104:46–52. https://doi.org/10.1016/j.jhin.2019.09.001.
45. Barsky EE, Williams KA, Priebe GP, Sawicki GS. 2017. Incident *Stenotrophomonas maltophilia* infection and lung function decline in cystic fibrosis. Pediatr Pulmonol 52:1276–1282. https://doi.org/10.1002/ppul.23781.
46. Berdah L, Taytard J, Leyronnas S, Clement A, Boelle P-Y, Corvol H. 2018. *Stenotrophomonas maltophilia*: a marker of lung disease severity. Pediatr Pulmonol 53:426–430. https://doi.org/10.1002/ppul.23943.
47. Chung H, Lieberman TD, Vargas SO, Flett KB, McAdam AJ, Priebe GP, Kishony R. 2017. Global and local selection acting on the pathogen *Stenotrophomonas maltophilia* in the human lung. Nat Commun 8:14078. https://doi.org/10.1038/ncomms14078.
48. Coburn B, Wang PW, Caballero JD, Clark ST, Brahma V, Donaldson S, Zhang Y, Surendra A, Gong Y, Tullis DE, Yau YCW, Waters VJ, Hwang DM, Guttman DS. 2015. Lung microbiota across age and disease stage in cystic fibrosis. Sci Rep 5:10241. https://doi.org/10.1038/srep10241.
49. Cogen J, Emerson J, Sanders DB, Ren C, Schechter MS, Gibson RL, Morgan W, Rosenfeld M, EPIC Study Group. 2015. Risk factors for lung function decline in a large cohort of young cystic fibrosis patients. Pediatr Pulmonol 50:763–770. https://doi.org/10.1002/ppul.23217.
50. Dalbøge CS, Hansen CR, Pressler T, Høiby N, Johansen HK. 2011. Chronic pulmonary infection with *Stenotrophomonas maltophilia* and lung function in patients with cystic fibrosis. J Cyst Fibros 10:318–325. https://doi.org/10.1016/j.jcf.2011.03.006.
51. Di Bonaventura G, Pompilio A, Zappacosta R, Petrucci F, Fiscarelli E, Rossi C, Piccolomini R. 2010. Role of excessive inflammatory response to *Stenotrophomonas maltophilia* lung infection in DBA/2 mice and implications for cystic fibrosis. Infect Immun 78:2466–2476. https://doi.org/10.1128/IAI.01391-09.
52. Díez-Aguilar M, Ekkelenkamp M, Morosini M-I, Merino I, de Dios Caballero J, Jones M, van Westreenen M, Tunney MM, Cantón R, Fluit AC. 2019. Antimicrobial susceptibility of non-fermenting Gram-negative pathogens isolated from cystic fibrosis patients. Int J Antimicrob Agents 53:84–88. https://doi.org/10.1016/j.ijantimicag.2018.09.001.
53. Geller M, Nunes CP, Oliveira L, Nigri R. 2018. *S. maltophilia* pneumonia: a case report. Respir Med Case Rep 24:44–45. https://doi.org/10.1016/j.rmcr.2018.04.004.
54. Granchelli AM, Adler FR, Keogh RH, Kartsonaki C, Cox DR, Liou TG. 2018. Microbial interactions in the cystic fibrosis airway. J Clin Microbiol 56:e00354-18. https://doi.org/10.1128/JCM.00354-18.
55. Guerci P, Bellut H, Mokhtari M, Gaudefroy J, Mongardon N, Charpentier C, Louis G, Tashk P, Dubost C, Ledochowski S, Kimmoun A, Godet T, Pottecher J, Lalot JM, Novy E, Hajage D, Bouglé A, AZUREA research network. 2019. Outcomes of *Stenotrophomonas maltophilia* hospital-acquired pneumonia in intensive care unit: a nationwide retrospective study. Crit Care 23:371. https://doi.org/10.1186/s13054-019-2649-5.
56. Hatziagorou E, Orenti A, Drevinek P, Kashirskaya N, Mei-Zahav M, De Boeck K, ECFSPR. 2020. Changing epidemiology of the respiratory bacteriology of patients with cystic fibrosis-data from the European cystic fibrosis society patient registry. J Cyst Fibros 19:376–383. https://doi.org/10.1016/j.jcf.2019.08.006.
57. Ibn Saied W, Merceron S, Schwebel C, Le Monnier A, Oziel J, Garrouste-Orgeas M, Marcotte G, Ruckly S, Souweine B, Darmon M, Bouadma L, de Montmollin E, Mourvillier B, Reignier J, Papazian L, Siami S, Azoulay E, Bédos J-P, Timsit J-F. 2020. Ventilator-associated pneumonia due to *Stenotrophomonas maltophilia*: risk factors and outcome. J Infect 80:279–285. https://doi.org/10.1016/j.jinf.2019.10.021.
58. Junge S, Görlich D, den Reijer M, Wiedemann B, Tümmler B, Ellemunter H, Dübbers A, Küster P, Ballmann M, Koerner-Rettberg C, Große-Onnebrink J, Heuer E, Sextro W, Mainz JG, Hammermann J, Riethmüller J, Graepler-Mainka U, Staab D, Wollschläger B, Szczepanski R, Schuster A, Tegtmeyer F-K, Sutharsan S, Wald A, Nofer J-R, van Wamel W, Becker K, Peters G, Kahl BC. 2016. Factors associated with worse lung function in cystic fibrosis patients with persistent *Staphylococcus aureus*. PLoS One 11:e0166220. https://doi.org/10.1371/journal.pone.0166220.
59. Kang YR, Cha YK, Kim JS, Lee EK, Oh JY, Bak SH, Yoon HJ. 2020. Imaging findings of *Stenotrophomonas maltophilia* pneumonia: emphasis on CT findings between immunocompromised and immunocompetent patients. Acta Radiol 61:903–909. https://doi.org/10.1177/0284185119885117.
60. McDaniel MS, Schoeb T, Swords WE. 2020. Cooperativity between *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa* during polymicrobial airway infections. Infect Immun 88:e00855-19. https://doi.org/10.1128/IAI.00855-19.
61. Marra R, Sgalla G, Richeldi L, Conte EG, Hill AT. 2020. Role of Stenotrophomonas maltophilia isolation in patients with non-CF bronchiectasis. QJM 113:726–730. https://doi.org/10.1093/qjmed/hcaa120.

62. Nys C, Cherabuddi K, Venugopalan V, Klinker KP. 2019. Clinical and microbiologic outcomes in patients with monomicrobial *Stenotrophomonas maltophilia* infections. Antimicro Agents Chemother 63:e00788-19. https://doi.org/10.1128/AAC.00788-19.
63. Patterson SB, Mende K, Li P, Lu D, Carson ML, Murray CK, Tribble DR, Blyth DM, IDCRP TIDOS Group. 2020. *Stenotrophomonas maltophilia* infections: clinical characteristics in a military trauma population. Diagn Microbiol Infect Dis 96:114953. https://doi.org/10.1016/j.diagmicrobio.2019.114953.
64. Penagos SC, Giraldo N, Vallejo C, McEwen O, Hidron A. 2020. First report of survival in two patients with hematologic malignancy and *Stenotrophomonas maltophilia* hemorrhagic pneumonia treated with trimethoprim-sulfamethoxazole-based combination antibiotic therapy. J Infect Chemother 26:397–399. https://doi.org/10.1016/j.jiac.2019.12.003.
65. Pompilio A, Crocetta V, Ghosh D, Chakrabarti M, Gherardi G, Vitali LA, Fiscarelli E, Di Bonaventura G. 2016. *Stenotrophomonas maltophilia* phenotypic and genotypic diversity during a 10-year colonization in the lungs of a cystic fibrosis patient. Front Microbiol 7:1551. https://doi.org/10.3389/fmicb.2016.01551.
66. Psoter KJ, De Roos AJ, Wakefield J, Mayer JD, Rosenfeld M. 2017. Seasonality of acquisition of respiratory bacterial pathogens in young children with cystic fibrosis. BMC Infect Dis 17:411. https://doi.org/10.1186/s12879-017-2511-9.
67. Salsgiver EL, Fink AK, Knapp EA, LiPuma JJ, Olivier KN, Marshall BC, Saiman L. 2016. Changing epidemiology of the respiratory bacteriology of patients with cystic fibrosis. Chest 149:390–400. https://doi.org/10.1378/chest.15-0676.
68. Scamardo MS, Dolce P, Esposito EP, Raimondi F, Triassi M, Zarrilli R. 2020. Trends, risk factors and outcomes of healthcare-associated infections in a neonatal intensive care unit in Italy during 2013–2017. Ital J Pediatr 46:34. https://doi.org/10.1186/s13052-020-0799-3.
69. Stanojevic S, Ratjen F, Stephens D, Lu A, Yau Y, Tullis E, Waters V. 2013. Factors influencing the acquisition of *Stenotrophomonas maltophilia* infection in cystic fibrosis patients. J Cyst Fibros 12:575–583. https://doi.org/10.1016/j.jcf.2013.05.009.
70. Tillman EM, Firmani SE, Ackerman VL, Slaven JE, Cristea AI. 2019. Evaluation of the treatment of *Stenotrophomonas maltophilia* in tracheostomy-dependent pediatric patients. J Pediatr Pharmacol Ther 24:510–516. https://doi.org/10.5863/1551-6776-24.6.510.
71. Wang L, Zhou W, Cao Y, Yang C, Liu H, Chen T, Chen L. 2020. Characteristics of *Stenotrophomonas maltophilia* infection in children in Sichuan, China, from 2010 to 2017. Medicine (Baltimore) 99:e19250. https://doi.org/10.1097/MD.0000000000019250.
72. Waters V, Atenafu EG, Lu A, Yau Y, Tullis E, Ratjen F. 2013. Chronic *Stenotrophomonas maltophilia* infection and mortality or lung transplantation in cystic fibrosis patients. J Cyst Fibros 12:482–486. https://doi.org/10.1016/j.jcf.2012.12.006.
73. Waters V, Yau Y, Prasad S, Lu A, Atenafu E, Crandall I, Tom S, Tullis E, Ratjen F. 2011. *Stenotrophomonas maltophilia* in cystic fibrosis. Serologic response and effect on lung disease. Am J Respir Crit Care Med 183:635–640. https://doi.org/10.1164/rccm.201009-1392OC.
74. Waters VJ, Gómez MI, Soong G, Amin S, Ernst RK, Prince A. 2007. Immunostimulatory properties of the emerging pathogen *Stenotrophomonas maltophilia*. Infect Immun 75:1698–1703. https://doi.org/10.1128/IAI.01469-06.
75. Wettlaufer J, Klingel M, Yau Y, Stanojevic S, Tullis E, Ratjen F, Waters V. 2017. Longitudinal study of *Stenotrophomonas maltophilia* antibody levels and outcomes in cystic fibrosis patients. J Cyst Fibros 16:58–63. https://doi.org/10.1016/j.jcf.2016.06.007.
76. Yin C, Yang W, Meng J, Lv Y, Wang J, Huang B. 2017. Co-infection of *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* in hospitalised pneumonia patients has a synergic and significant impact on clinical outcomes. Eur J Clin Microbiol Infect Dis 36:2231–2235. https://doi.org/10.1007/s10096-017-3050-4.
77. Agarwal AK, Aggarwal K, Samanta R, Angrup A, Biswal M, Ray P, Dogra M, Katoch D, Bansal R, Singh R, Dogra MR, Gupta V. 2019. Cluster endophthalmitis due to *Stenotrophomonas maltophilia* following intravitreal bevacizumab: outcomes of patients from North India. Br J Ophthalmol 103:1278–1283. https://doi.org/10.1136/bjophthalmol-2018-313131.
78. Angrup A, Krishnamoorthi S, Biswal M, Gautam V, Ray P, Agarwal A, Dogra MR, Singh R, Katoch D, Gupta V. 2018. Utility of MALDI-TOF mass spectrometry in an outbreak investigation of acute endophthalmitis following intravitreal injection. J Hosp Infect 100:e253–e256. https://doi.org/10.1016/j.jhin.2018.03.032.
79. Beri S, Shandil A, Garg R. 2017. *Stenotrophomonas maltophilia*: an emerging entity for cluster endophthalmitis. Indian J Ophthalmol 65:1166–1171. https://doi.org/10.4103/ijo.IJO_314_17.
80. Chang JS, Flynn HW, Jr, Miller D, Smiddy WE. 2013. *Stenotrophomonas maltophilia* endophthalmitis following cataract surgery: clinical and microbiological results. Clin Ophthalmol 7:771–777. https://doi.org/10.2147/OPTH.S39608.
81. Chhablani J, Sudhalkar A, Jindal A, Das T, Motukupally SR, Sharma S, Pathengay A, Flynn HW, Jr. 2014. *Stenotrophomonas maltophilia* endogenous endophthalmitis: clinical presentation, antibiotic susceptibility, and outcomes. Clin Ophthalmol 8:1523–1526. https://doi.org/10.2147/OPTH.S67396.
82. Hogg HDJ, Siah WF, Okonkwo A, Narayanan M, Figueiredo FC. 2019. *Stenotrophomonas maltophilia*—a case series of a rare keratitis affecting patients with bandage contact. Eye Contact Lens 45:e1–e4. https://doi.org/10.1097/ICL.0000000000000479.
83. Holifield K, Lazzaro DR. 2011. Case report: spontaneous *Stenotrophomonas maltophilia* keratitis in a diabetic patient. Eye Contact Lens 37:326–327. https://doi.org/10.1097/ICL.0b013e3182146e26.
84. Karaca I, Barut Selver O, Palamar M, Egrilmez S, Aydemir S, Yagci A. 2019. Contact lens-associated microbial keratitis in a tertiary eye care center in Turkey. Eye Contact Lens 46:110–115. https://doi.org/10.1097/ICL.0000000000000617.
85. Inviati A, Pellegrino DM, Schifano D. 2018. Severe hepatic abscess: conservative treatment of multi-organ infection by *Stenotrophomonas maltophilia*. A case report. Ann Med Surg (Lond) 34:62–65. https://doi.org/10.1016/j.amsu.2018.09.001.
86. Ji Y, Jiang C, Ji J, Luo Y, Jiang Y, Lu Y. 2015. Post-cataract endophthalmitis caused by multidrug-resistant *Stenotrophomonas maltophilia*: clinical features and risk factors. BMC Ophthalmol 15:14. https://doi.org/10.1186/1471-2415-15-14.
87. Mahendradas P, Avadhani K, ANandula V, Shetty R. 2012. Unilateral conjunctival ulcer due to *Stenotrophomonas maltophilia* infection. Indian J Ophthalmol 60:134–136. https://doi.org/10.4103/0301-4738.94056.
88. Majtanova N, Vodrazkova E, Kurilova V, Horniackova M, Cernak M, Cernak A, Majtan J. 2015. Complementary treatment of contact lens-induced corneal ulcer using honey: a case report. Cont Lens Anterior Eye 38:61–63. https://doi.org/10.1016/j.clae.2014.09.004.
89. Palioura S, Gibbons A, Miller D, O'brien TP, Alfonso EC, Spierer O. 2018. Clinical features, antibiotic susceptibility profile, and outcomes of infectious keratitis caused by *Stenotrophomonas maltophilia*. Cornea 37:326–330. https://doi.org/10.1097/ICO.0000000000001486.
90. Rossetto JD, Cavuoto KM, Osigian CJ, Chang TCP, Miller D, Capo H, Spierer O. 2017. Paediatric infectious keratitis: a case series of 107 children presenting to a tertiary referral centre. Br J Ophthalmol 101:1488–1492. https://doi.org/10.1136/bjophthalmol-2016-310119.
91. Son SW, Kim HJ, Seo JW. 2011. A case of *Stenotrophomonas maltophilia* keratitis effectively treated with moxifloxacin. Korean J Ophthalmol 25:349–351. https://doi.org/10.3341/kjo.2011.25.5.349.
92. Spierer O, Miller D, O'Brien TP. 2018. Comparative activity of antimicrobials against *Pseudomonas aeruginosa*, *Achromobacter xylosoxidans* and *Stenotrophomonas maltophilia* keratitis isolates. Br J Ophthalmol 102:708–712. https://doi.org/10.1136/bjophthalmol-2017-311751.
93. Taskiran Comez A, Koklu A, Akcali A. 2014. Chronic dacryocystitis secondary to *Stenotrophomonas maltophilia* and *Staphylococcus aureus* mixed infection. BMJ Case Rep 2014:bcr2014203642. https://doi.org/10.1136/bcr-2014-203642.
94. Ting DSJ, Bignardi G, Koerner R, Irion LD, Johnson E, Morgan SJ, Ghosh S. 2019. Polymicrobial keratitis with *Cryptococcus curvatus*, *Candida parapsilosis*, and *Stenotrophomonas maltophilia* after penetrating keratoplasty: a rare case report with literature review. Eye Contact Lens 45:e5–e10. https://doi.org/10.1097/ICL.0000000000000517.
95. Williams MA, Gramajo AL, Colombres GA, Caeiro JP, Juárez CP, Luna JD. 2014. *Stenotrophomonas maltophilia* endophthalmitis caused by surgical equipment contamination: an emerging nosocomial infection. J Ophthalmic Vis Res 9:383–387. https://doi.org/10.4103/2008-322X.143381.
96. Wu A-L, Yeh L-K, Ma DHK, Chen PYF, Lin H-C, Sun C-C, Tan H-Y, Chen H-C, Chen S-Y, Hsiao C-H. 2016. Clinical characteristics of *Stenotrophomonas maltophilia* keratitis. Cornea 35:795–800. https://doi.org/10.1097/ICO.0000000000000855.

97. Alat I, Kılıç AT, Çelik E. 2019. Replacement of the native mitral valve due to endocarditis caused by *Stenotrophomonas maltophilia*. Braz J Cardiovasc Surg 34:615–617. https://doi.org/10.21470/1678-9741-2019-0300.
98. Kucukates E, Gultekin N, Bagdatli Y. 2013. Cases of active infective endocarditis in a university hospital during a 10-year period. J Pak Med Assoc 63:1163–1167.
99. Satish M, Mumtaz MA, Bittner MJ, Valenta C. 2019. *Stenotrophomonas maltophilia* endocarditis of an implantable cardioverter defibrillator lead. Cureus 11:e4165. https://doi.org/10.7759/cureus.4165.
100. Shah S, King M, Rose L. 2019. Medical management of endocarditis caused by *Stenotrophomonas maltophilia*: a case report. J Pharm Pract 32:683–686. https://doi.org/10.1177/0897190018764957.
101. Adsul NM, Panigrahi V, Acharya S, Kalra KL, Chahal RS. 2020. *Stenotrophomonas maltophilia* spondylodiscitis following lumbar microdiscectomy mimicking a cotton granuloma: a case report and literature review. Surg Neurol Int 11:28. https://doi.org/10.25259/SNI_23_2020.
102. Ibrahim J, Hamwi N, Rabei H, Abdelghafar M, Al-Dulaimi Z, Al Tatari H. 2018. *Stenotrophomonas maltophilia* meningitis in a term healthy neonate: a case report and literature review. Case Rep Pediatr 2018:1543934. https://doi.org/10.1155/2018/1543934.
103. Sood S, Vaid VK, Bhartiya H. 2013. Meningitis due to *Stenotrophomonas maltophilia* after a neurosurgical procedure. J Clin Diagn Res 7:1696–1697. https://doi.org/10.7860/JCDR/2013/5614.3248.
104. Rémi J, Loesch-Biffar AM, Mehrkens J, Thon N, Seelos K, Pfister H-W. 2019. *Stenotrophomonas maltophilia* brain abscesses after implantation of motor cortex stimulator. J Neurol Sci 400:32–33. https://doi.org/10.1016/j.jns.2019.03.010.
105. Wang G, Xu N, Yang L, Zheng F, Sai L, Zhou J, Yang S. 2019. Community acquired *Stenotrophomonas maltophilia* discitis: diagnosis aided by shotgun metagenomic sequencing. Int J Infect Dis 81:1–3. https://doi.org/10.1016/j.ijid.2019.01.032.
106. Kaito S, Sekiya N, Najima Y, Sano N, Horiguchi S, Kakihana K, Hishima T, Ohashi K. 2018. Fatal neutropenic enterocolitis caused by *Stenotrophomonas maltophilia*: a rare and underrecognized entity. Intern Med 57:3667–3671. https://doi.org/10.2169/internalmedicine.1227-18.
107. Lim DR, Kuk JC, Kim T, Shin EJ. 2017. Unusual case of rapid growing intraabdominal abscess caused by *Stenotrophomonas maltophilia* after laparoscopic appendectomy due to perforated appendicitis: a case report. Medicine (Baltimore) 96:e6913. https://doi.org/10.1097/MD.0000000000006913.
108. Millán-Díaz B, González-Tabarés L, Cobelo-Casas C, López-Vázquez M, Calviño-Varela J. 2017. *Stenotrophomonas maltophilia*: a rare cause of peritonitis in capd patients. Nefrologia 37:646–647. https://doi.org/10.1016/j.nefro.2017.03.018.
109. Prates M, Fernandes F, Proença F, Mussá Y, Tavares A, Pereira A. 2020. Oral infection caused by *Stenotrophomonas maltophilia*: a rare presentation of an emerging opportunistic pathogen. Case Rep Infect Dis 2020:6346120. https://doi.org/10.1155/2020/6346120.
110. Ahmed M, Syed R, More YI, Basha SI. 2019. *Stenotrophomonas* skull base osteomyelitis presenting as necrotizing otitis externa: unmasking by CT and MRI – case report and review. Radiol Case Rep 14:1241–1245. https://doi.org/10.1016/j.radcr.2019.07.018.
111. Ali U, Abbasi SA, Kaleem F, Aftab I, Butt T. 2017. Outbreak of extensively drug resistant *Stenotrophomonas maltophilia* in burn unit. J Ayub Med Coll Abbottabad 29:686–688.
112. Baumrin E, Piette EW, Micheletti RG. 2017. *Stenotrophomonas maltophilia*: an emerging multidrug-resistant opportunistic pathogen in the immunocompromised host. BMJ Case Rep 2017:bcr2017221053. https://doi.org/10.1136/bcr-2017-221053.
113. Chesnutis EJ, Ng A, Kruse D, Stone PA. 2018. *Stenotrophomonas maltophilia*: a rare case of osteomyelitis after an open distal tibial fracture. J Foot Ankle Surg 57:1037–1041. https://doi.org/10.1053/j.jfas.2018.03.001.
114. Chiu LQ, Wang W. 2013. A case of unusual Gram-negative bacilli septic arthritis in an immunocompetent patient. Singapore Med J 54:e164–e168. https://doi.org/10.11622/smedj.2013162.
115. Frietsch JJ, Winkelmann N, Hunstig F, Schnetzke U, Hammersen FJ, Dönicke T, Lenz M, Gras F, Scholl S, Hochhaus A, Hilgendorf I. 2019. A mosquito bite with devastating complications in an immunocompromised patient. Case Rep Oncol 12:22–28. https://doi.org/10.1159/000495878.
116. Gao Y, Minca EC, Procop GW, Bergfeld WF. 2016. *Stenotrophomonas maltophila* cellulitis in an immunocompromised patient presenting with purpura, diagnosed on skin biopsy. J Cutan Pathol 43:1017–1020. https://doi.org/10.1111/cup.12765.
117. Jabbour J-F, Sharara SL, Kanj SS. 2020. Treatment of multidrug-resistant Gram-negative skin and soft tissue infections. Curr Opin Infect Dis 33:146–154. https://doi.org/10.1097/QCO.0000000000000635.
118. Karan NB, Kose R, Kalyoncu A, Sekeryapan B, Oter K, Findik H, Yurdakul C. 2019. Fatal orbital necrotizing fasciitis secondary to *Stenotrophomonas maltophilia* associated stomatitis. J Stomatol Oral Maxillofac Surg 120:260–262. https://doi.org/10.1016/j.jormas.2018.11.004.
119. Kounis NG, Soufras GD, Hahalis G. 2013. Stent hypersensitivity and infection in sinus cavities. Allergy Rhinol (Providence) 4:e162–e165. https://doi.org/10.2500/ar.2013.4.0071.
120. López-Cárdenas S, Pérez-Cortés S, Reguera-García A, Alados-Arboledas JC. 2012. Community acquired *Stenotrophomonas maltophilia* soft-tissue infection in a previously healthy patient. Med Clin (Barc) 138:411–412. https://doi.org/10.1016/j.medcli.2011.07.002.
121. Loupa CV, Meimeti E, Voyatzoglou E, Donou A, Koutsantoniou E, Lafoyanni S. 2018. Successful nonsurgical therapy of a diabetic foot osteomyelitis in a patient with peripheral artery disease with almost complete radiological restoration. BMC Res Notes 11:579. https://doi.org/10.1186/s13104-018-3694-x.
122. Stens O, Wardi G, Kinney M, Shin S, Papamatheakis D. 2018. *Stenotrophomonas maltophilia* necrotizing soft tissue infection in an immunocompromised patient. Case Rep Crit Care 2018:1475730. https://doi.org/10.1155/2018/1475730.
123. Trignano E, Manzo MJ, Fallico N, Maffei M, Marongiu F, Campus GV, Rubino C. 2014. First report of digital skin ulcer with *Stenotrophomonas maltophilia* infection in an immunocompetent patient. In Vivo 28:259–261.
124. Alcaraz E, Garcia C, Papalia M, Vay C, Friedman L, Passerini de Rossi B. 2018. *Stenotrophomonas maltophilia* isolated from patients exposed to invasive devices in a university hospital in Argentina: molecular typing, susceptibility and detection of potential virulence factors. J Med Microbiol 67:992–1002. https://doi.org/10.1099/jmm.0.000764.
125. Gregory ER, Osborne SB, Gardner BM, Broughton RA. 2019. Trimethoprim/sulfamethoxazole and moxifloxacin therapy for a pediatric *Stenotrophomonas maltophilia* ventriculoperitoneal shunt infection. J Pediatr Pharmacol Ther 24:61–65. https://doi.org/10.5863/1551-6776-24.1.61.
126. Kusaba T, Kirita Y, Ishida R, Matsuoka E, Nakayama M, Uchiyama H, Kajita Y. 2012. Morphological analysis of biofilm of peritoneal dialysis catheter in refractory peritonitis patient. CEN Case Rep 1:50–54. https://doi.org/10.1007/s13730-012-0012-7.
127. Thet MK, Pelobello MLF, Das M, Alhaji MM, Chong VH, Khalil MAM, Chinniah T, Tan J. 2019. Outbreak of nonfermentative Gram-negative bacteria (*Ralstonia pickettii* and *Stenotrophomonas maltophilia*) in a hemodialysis center. Hemodial Int 23:E83–E89. https://doi.org/10.1111/hdi.12722.
128. Zhang L, Morrison M, Cuív PÓ, Evans P, Rickard CM. 2013. Genome sequence of *Stenotrophomonas maltophilia* strain AU12-09, isolated from an intravascular catheter. Genome Announc 1:e00195-13. https://doi.org/10.1128/genomeA.00195-13.
129. Sarmand N, Gompelmann D, Kontogianni K, Polke M, Herth FJF, Eberhardt R. 2018. New bacterial growth in bronchial secretions after bronchoscopic valve implantation. Int J Chron Obstruct Pulmon Dis 13:565–570. https://doi.org/10.2147/COPD.S148196.
130. Saugel B, Eschermann K, Hoffmann R, Hapfelmeier A, Schultheiss C, Phillip V, Eyer F, Laugwitz KL, Schmid RM, Huber W. 2012. *Stenotrophomonas maltophilia* in the respiratory tract of medical intensive care unit patients. Eur J Clin Microbiol Infect Dis 31:1419–1428. https://doi.org/10.1007/s10096-011-1459-8.
131. 2015. Epidemiology of infection and current guidelines for infection prevention in cystic fibrosis patients. J Hosp Infect 89:309–313. https://doi.org/10.1016/j.jhin.2015.02.005.
132. Wainwright CE, France MW, O'Rourke P, Anuj S, Kidd TJ, Nissen MD, Sloots TP, Coulter C, Ristovski Z, Hargreaves M, Rose BR, Harbour C, Bell SC, Fennelly KP. 2009. Cough-generated aerosols of *Pseudomonas aeruginosa* and other Gram-negative bacteria from patients with cystic fibrosis. Thorax 64:926–931. https://doi.org/10.1136/thx.2008.112466.
133. Pompilio A, Ciavardelli D, Crocetta V, Consalvo A, Zappacosta R, Di Ilio C, Di Bonaventura G. 2014. *Stenotrophomonas maltophilia* virulence and specific variations in trace elements during acute lung infection: implications in cystic fibrosis. PLoS One 9:e88769. https://doi.org/10.1371/journal.pone.0088769.
134. Stoyanova GP, Strateva TV, Atanasova ST, Miteva DS, Papochieva VE, Perenovska PI. 2016. Pulmonary exacerbation due to colistin-resistant *Stenotrophomonas maltophilia* in a Bulgarian cystic fibrosis patient. Folia Med (Plovdiv) 58:136–140. https://doi.org/10.1515/folmed-2016-0014.

135. Linnane B, Collins L, Bussmann N, O'Connell NH, Dunne CP. 2017. Medical devices for cystic fibrosis care may be portable reservoirs of potential pathogens. J Hosp Infect 96:397–400. https://doi.org/10.1016/j.jhin.2017.04.015.
136. Liu B, Tong S. 2019. An investigation of *Stenotrophomonas maltophilia*-positive culture caused by fiberoptic bronchoscope contamination. BMC Infect Dis 19:1072. https://doi.org/10.1186/s12879-019-4670-3.
137. Ofstead CL, Heymann OL, Quick MR, Eiland JE, Wetzler HP. 2018. Residual moisture and waterborne pathogens inside flexible endoscopes: evidence from a multisite study of endoscope drying effectiveness. Am J Infect Control 46:689–696. https://doi.org/10.1016/j.ajic.2018.03.002.
138. de Abreu PM, Farias PG, Paiva GS, Almeida AM, Morais PV. 2014. Persistence of microbial communities including *Pseudomonas aeruginosa* in a hospital environment: a potential health hazard. BMC Microbiol 14:118. https://doi.org/10.1186/1471-2180-14-118.
139. Vincenti S, Quaranta G, De Meo C, Bruno S, Ficarra MG, Carovillano S, Ricciardi W, Laurenti P. 2014. Non-fermentative Gram-negative bacteria in hospital tap water and water used for haemodialysis and bronchoscope flushing: prevalence and distribution of antibiotic resistant strains. Sci Total Environ 499:47–54. https://doi.org/10.1016/j.scitotenv.2014.08.041.
140. Jarząb N, Walczak M. 2017. The presence of biofilm forming microorganisms on hydrotherapy equipment and facilities. J Water Health 15:923–931. https://doi.org/10.2166/wh.2017.025.
141. Li Y-C, Lin H-L, Liao F-C, Wang S-S, Chang H-C, Hsu H-F, Chen S-H, Wan G-H. 2018. Potential risk for bacterial contamination in conventional reused ventilator systems and disposable closed ventilator-suction systems. PLoS One 13:e0194246. https://doi.org/10.1371/journal.pone.0194246.
142. Romano-Bertrand S, Evrevin M, Dupont C, Frapier J-M, Sinquet J-C, Bousquet E, Albat B, Jumas-Bilak E. 2018. Persistent contamination of heater-cooler units for extracorporeal circulation cured by chlorhexidine-alcohol in water tanks. J Hosp Infect 99:290–294. https://doi.org/10.1016/j.jhin.2018.01.005.
143. Guyot A, Turton JF, Garner D. 2013. Outbreak of *Stenotrophomonas maltophilia* on an intensive care unit. J Hosp Infect 85:303–307. https://doi.org/10.1016/j.jhin.2013.09.007.
144. Heller D, Helmerhorst EJ, Gower AC, Siqueira WL, Paster BJ, Oppenheim FG. 2016. Microbial diversity in the early *in vivo*-formed dental biofilm. Appl Environ Microbiol 82:1881–1888. https://doi.org/10.1128/AEM.03984-15.
145. Battaini A, La Scola B, Yin GHW, Hoffart L, Drancourt M. 2018. Amebaborne *Attilina massiliensis* keratitis. Emerg Infect Dis 24:387–389. https://doi.org/10.3201/eid2402.170541.
146. King P, Pham LK, Waltz S, Sphar D, Yamamoto RT, Conrad D, Taplitz R, Torriani F, Forsyth RA. 2016. Longitudinal metagenomic analysis of hospital air identifies clinically relevant microbes. PLoS One 11:e0160124. https://doi.org/10.1371/journal.pone.0160124.
147. Ali B. 2019. Functional and genetic diversity of bacteria associated with the surfaces of agronomic plants. Plants 8:91. https://doi.org/10.3390/plants8040091.
148. Cleto S, Matos S, Kluskens L, Vieira MJ. 2012. Characterization of contaminants from a sanitized milk processing plant. PLoS One 7:e40189. https://doi.org/10.1371/journal.pone.0040189.
149. Coton M, Delbés-Paus C, Irlinger F, Desmasures N, Le Fleche A, Stahl V, Montel M-C, Coton E. 2012. Diversity and assessment of potential risk factors of Gram-negative isolates associated with French cheeses. Food Microbiol 29:88–98. https://doi.org/10.1016/j.fm.2011.08.020.
150. Fröhling A, Rademacher A, Rumpold B, Klocke M, Schlüter O. 2018. Screening of microbial communities associated with endive lettuce during postharvest processing on industrial scale. Heliyon 4:e00671. https://doi.org/10.1016/j.heliyon.2018.e00671.
151. Gaglio R, Francesca N, Di Gerlando R, Mahony J, De Martino S, Stucchi C, Moschetti G, Settanni L. 2017. Enteric bacteria of food ice and their survival in alcoholic beverages and soft drinks. Food Microbiol 67:17–22. https://doi.org/10.1016/j.fm.2017.04.020.
152. Hagi T, Sasaki K, Aso H, Nomura M. 2013. Adhesive properties of predominant bacteria in raw cow's milk to bovine mammary gland epithelial cells. Folia Microbiol (Praha) 58:515–522. https://doi.org/10.1007/s12223-013-0240-z.
153. Karumathil DP, Yin H-B, Kollanoor-Johny A, Venkitanarayanan K. 2016. Prevalence of multidrug-resistant bacteria on fresh vegetables collected from farmers' markets in Connecticut. J Food Prot 79:1446–1451. https://doi.org/10.4315/0362-028X.JFP-15-548.
154. Li D, Wong CH, Seet MF, Kuan N. 2019. Isolation, characterization, and inactivation of *Stenotrophomonas maltophilia* from leafy green vegetables and urban agriculture systems. Front Microbiol 10:2718. https://doi.org/10.3389/fmicb.2019.02718.
155. Lin L, Wang S-F, Yang T-Y, Hung W-C, Chan M-Y, Tseng S-P. 2017. Antimicrobial resistance and genetic diversity in ceftazidime non-susceptible bacterial pathogens from ready-to-eat street foods in three Taiwanese cities. Sci Rep 7:15515. https://doi.org/10.1038/s41598-017-15627-8.
156. Nakayama T, Ha NC, Quoc Le P, Kawahara R, Kumeda Y, Sumimura Y, Yamamoto Y. 2017. Consumption of edible ice contaminated with *Acinetobacter*, *Pseudomonas*, and *Stenotrophomonas* is a risk factor for fecal colonization with extended-spectrum β-lactamase-producing *Escherichia coli* in Vietnam. J Water Health 15:813–822. https://doi.org/10.2166/wh.2017.054.
157. Okuno NT, Freire IR, Segundo RTRS, Silva CR, Marin VA. 2018. Polymerase chain reaction assay for detection of *Stenotrophomonas maltophilia* in cheese samples based on the *smeT* gene. Curr Microbiol 75:1555–1559. https://doi.org/10.1007/s00284-018-1559-0.
158. Todaro M, Francesca N, Reale S, Moschetti G, Vitale F, Settanni L. 2011. Effect of salting technologies on the chemical and microbiological characteristics of PDO Pecorino Siciliano cheese. Eur Food Res Technol 233:931–940. https://doi.org/10.1007/s00217-011-1593-7.
159. Yamamoto S, Nakayama T, Asakura H. 2020. Draft genome sequence of *Stenotrophomonas maltophilia* CRB139-1, isolated from poultry meat in Japan. Microbiol Resour Announc 9:e00075-20. https://doi.org/10.1128/MRA.00075-20.
160. Zupančič J, Turk M, Črnigoj M, Ambrožič Avguštin J, Gunde-Cimerman N. 2019. The dishwasher rubber seal acts as a reservoir of bacteria in the home environment. BMC Microbiol 19:300. https://doi.org/10.1186/s12866-019-1674-5.
161. Alouache S, Kada M, Messai Y, Estepa V, Torres C, Bakour R. 2012. Antibiotic resistance and extended-spectrum β-lactamases in isolated bacteria from seawater of Algiers beaches (Algeria). Microbes Environ 27:80–86. https://doi.org/10.1264/jsme2.me11266.
162. Dai D, Raskin L, Xi C. 2017. The effect of interactions between a bacterial strain isolated from drinking water and a pathogen surrogate on biofilms formation diverged under static vs flow conditions. J Appl Microbiol 123:1614–1627. https://doi.org/10.1111/jam.13596.
163. Glady-Croue J, Niu X-Z, Ramsay JP, Watkin E, Murphy RJT, Croue J-P. 2018. Survival of antibiotic resistant bacteria following artificial solar radiation of secondary wastewater effluent. Sci Total Environ 626:1005–1011. https://doi.org/10.1016/j.scitotenv.2018.01.101.
164. Gomes IB, Lemos M, Mathieu L, Simões M, Simões LC. 2018. The action of chemical and mechanical stresses on single and dual species biofilm removal of drinking water bacteria. Sci Total Environ 631–632:987–993. https://doi.org/10.1016/j.scitotenv.2018.03.042.
165. Gomes IB, Querido MM, Teixeira JP, Pereira CC, Simões LC, Simões M. 2019. Prolonged exposure of *Stenotrophomonas maltophilia* biofilms to trace levels of clofibric acid alters antimicrobial tolerance and virulence. Chemosphere 235:327–335. https://doi.org/10.1016/j.chemosphere.2019.06.184.
166. Gomes IB, Simões LC, Simões M. 2018. The effects of emerging environmental contaminants on *Stenotrophomonas maltophilia* isolated from drinking water in planktonic and sessile states. Sci Total Environ 643:1348–1356. https://doi.org/10.1016/j.scitotenv.2018.06.263.
167. Gomes IB, Simões LC, Simões M. 2020. Influence of surface copper content on *Stenotrophomonas maltophilia* biofilm control using chlorine and mechanical stress. Biofouling 36:1–13. https://doi.org/10.1080/08927014.2019.1708334.
168. Gomes IB, Simões M, Simões LC. 2016. The effects of sodium hypochlorite against selected drinking water-isolated bacteria in planktonic and sessile states. Sci Total Environ 565:40–48. https://doi.org/10.1016/j.scitotenv.2016.04.136.
169. Gomes TS, Vaccaro L, Magnet A, Izquierdo F, Ollero D, Martínez-Fernández C, Mayo L, Moran M, Pozuelo MJ, Fenoy S, Hurtado C, Del Águila C. 2020. Presence and interaction of free-living amoebae and amoeba-resisting bacteria in water from drinking water treatment plants. Sci Total Environ 719:137080. https://doi.org/10.1016/j.scitotenv.2020.137080.
170. Kim Y-J, Park J-H, Seo K-H. 2018. Presence of *Stenotrophomonas maltophilia* exhibiting high genetic similarity to clinical isolates in final effluents of pig farm wastewater treatment plants. Int J Hyg Environ Health 221:300–307. https://doi.org/10.1016/j.ijheh.2017.12.002.
171. Kregiel D, Rygala A, Kolesinska B, Nowacka M, Herc AS, Kowalewska A. 2019. Antimicrobial and antibiofilm *N*-acetyl-L-cysteine grafted siloxane

polymers with potential for use in water systems. Int J Mol Sci 20:2011. https://doi.org/10.3390/ijms20082011.

172. Maes S, Vackier T, Nguyen Huu S, Heyndrickx M, Steenackers H, Sampers I, Raes K, Verplaetse A, De Reu K. 2019. Occurrence and characterisation of biofilms in drinking water systems of broiler houses. BMC Microbiol 19:77. https://doi.org/10.1186/s12866-019-1451-5.
173. Martin MS, Santos IC, Carlton DD, Jr, Stigler-Granados P, Hildenbrand ZL, Schug KA. 2018. Characterization of bacterial diversity in contaminated groundwater using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Sci Total Environ 622–623:1562–1571. https://doi.org/10.1016/j.scitotenv.2017.10.027.
174. Tacão M, Correia A, Henriques IS. 2015. Low prevalence of carbapenem-resistant bacteria in river water: resistance is mostly related to intrinsic mechanisms. Microb Drug Resist 21:497–506. https://doi.org/10.1089/mdr.2015.0072.
175. Bodilis J, Youenou B, Briolay J, Brothier E, Favre-Bonté S, Nazaret S. 2016. Draft genome sequences of *Stenotrophomonas maltophilia* strains Sm32COP, Sm41DVV, Sm46PAILV, SmF3, SmF22, SmSOFb1, and SmCVFa1, isolated from different manures in France. Genome Announc 4:e00841-16. https://doi.org/10.1128/genomeA.00841-16.
176. Elufisan TO, Lozano L, Bustos P, Rodríguez-Luna IC, Sánchez-Varela A, Oyedara OO, Villalobos-López MÁ, Guo X. 2019. Complete genome sequence of *Stenotrophomonas maltophilia* strain SVIA2, isolated from crude oil-contaminated soil in Tabasco. Microbiol Resour Announc 8: e00529-19. https://doi.org/10.1128/MRA.00529-19.
177. Furlan JPR, Pitondo-Silva A, Stehling EG. 2018. Detection of bla_{NDM-1} in *Stenotrophomonas maltophilia* isolated from Brazilian soil. Mem Inst Oswaldo Cruz 113:e170558. https://doi.org/10.1590/0074-02760170558.
178. Furlan JPR, Sanchez DG, Gallo IFL, Stehling EG. 2019. Characterization of acquired antimicrobial resistance genes in environmental *Stenotrophomonas maltophilia* isolates from Brazil. Microb Drug Resist 25:475–479. https://doi.org/10.1089/mdr.2018.0216.
179. Bhanderi BB, Jhala MK, Ahir VB, Bhatt VD, Joshi CG. 2014. Cultural and metagenomic based identification of a microbiome from subclinical mastitis in cows. Vet Arh 84:215–228.
180. Domosławska A, Zduńczyk S, Jurczak A, Janowski T. 2017. *Stenotrophomonas maltophilia* isolated from prostatic fluid as an infertility factor in a male dog. Andrologia 49:e12769. https://doi.org/10.1111/and.12769.
181. Gentilini F, Turba ME, Pasquali F, Mion D, Romagnoli N, Zambon E, Terni D, Peirano G, Pitout JDD, Parisi A, Sambri V, Zanoni RG. 2018. Hospitalized pets as a source of carbapenem-resistance. Front Microbiol 9:2872. https://doi.org/10.3389/fmicb.2018.02872.
182. Hou D, Bi Y, Sun H, Yang J, Fu G, Sun Y, Liu J, Pu J. 2012. Identification of swine influenza A virus and *Stenotrophomonas maltophilia* co-infection in Chinese pigs. Virol J 9:169. https://doi.org/10.1186/1743-422X-9-169.
183. Jayol A, Corlouer C, Haenni M, Darty M, Maillard K, Desroches M, Lamy B, Jumas-Bilak E, Madec J-Y, Decousser J-W. 2018. Are animals a source of *Stenotrophomonas maltophilia* in human infections? Contributions of a nationwide molecular study. Eur J Clin Microbiol Infect Dis 37:1039–1045. https://doi.org/10.1007/s10096-018-3203-0.
184. Ohnishi M, Sawada T, Marumo K, Harada K, Hirose K, Shimizu A, Hayashimoto M, Sato R, Uchida N, Kato H. 2012. Antimicrobial susceptibility and genetic relatedness of bovine *Stenotrophomonas maltophilia* isolates from a mastitis outbreak. Lett Appl Microbiol 54:572–576. https://doi.org/10.1111/j.1472-765X.2012.03246.x.
185. Winther L, Andersen RM, Baptiste KE, Aalbæk B, Guardabassi L. 2010. Association of *Stenotrophomonas maltophilia* infection with lower airway disease in the horse: a retrospective case series. Vet J 186:358–363. https://doi.org/10.1016/j.tvjl.2009.08.026.
186. Jacobs L, McMahon BH, Berendzen J, Longmire J, Gleasner C, Hengartner NW, Vuyisich M, Cohn JR, Jenkins M, Bartlow AW, Fair JM. 2019. California condor microbiomes: bacterial variety and functional properties in captive-bred individuals. PLoS One 14:e0225858. https://doi.org/10.1371/journal.pone.0225858.
187. Jacobs L, McMahon BH, Berendzen J, Longmire J, Gleasner C, Hengartner NW, Vuyisich M, Cohn JD, Jenkins M, Bartlow AW, Fair JM. 2020. Correction: California condor microbiomes: bacterial variety and functional properties in captive-bred individuals. PLoS One 15:e0230738. https://doi.org/10.371/journal.pone.0230738.
188. Abraham TJ, Pradipta P, Adikesavalu H, Avijit P, Banerjee S. 2016. *Stenotrophomonas maltophila* as an opportunistic pathogen in cultured African catfish *Clarias gariepinus* (Burchell, 1822). Aquaculture 450:168–172. https://doi.org/10.1016/j.aquaculture.2015.07.015.
189. Torabi Delshad S, Soltanian S, Sharifiyazdi H, Haghkhah M, Bossier P. 2018. Identification of *N*-acyl homoserine lactone-degrading bacteria isolated from rainbow trout (*Oncorhynchus mykiss*). J Appl Microbiol 125:356–369. https://doi.org/10.1111/jam.13891.
190. Wang Q, Ji F, Wang J, Jiang B, Li L, An L, Li Y, Bao Y. 2016. Characterization of a salt-activated protease with temperature-dependent secretion in *Stenotrophomonas maltophilia* FF11 isolated from frozen Antarctic krill. J Ind Microbiol Biotechnol 43:829–840. https://doi.org/10.1007/s10295-016-1749-3.
191. Wang X, Peng L, Wang K, Wang J, He Y, Wang E, Chen D, Ouyang P, Geng Y, Huang X. 2016. The outer membrane proteins of *Stenotrophomonas maltophilia* are potential vaccine candidates for channel catfish (*Ictalurus punctatus*). Fish Shellfish Immunol 57:318–324. https://doi.org/10.1016/j.fsi.2016.08.054.
192. Di Ianni F, Dodi PL, Cabassi CS, Pelizzone I, Sala A, Cavirani S, Parmigiani E, Quintavalla F, Taddei S. 2015. Conjunctival flora of clinically normal and diseased turtles and tortoises. BMC Vet Res 11:91. https://doi.org/10.1186/s12917-015-0405-x.
193. Fitzgerald KT, Shipley BK, Newquist KL, Vera R, Flood AA. 2013. Additional observations and notes on the natural history of the prairie rattlesnake (*Crotalus viridis*) in Colorado. Top Companion Anim Med 28:167–176. https://doi.org/10.1053/j.tcam.2013.09.008.
194. Nickerson CA, Ott CM, Castro SL, Garcia VM, Molina TC, Briggler JT, Pitt AL, Tavano JJ, Byram JK, Barrila J, Nickerson MA. 2011. Evaluation of microorganisms cultured from injured and repressed tissue regeneration sites in endangered giant aquatic Ozark Hellbender salamanders. PLoS One 6:e28906. https://doi.org/10.1371/journal.pone.0028906.
195. O'Connell D, Mruk K, Rocheleau JM, Kobertz WR. 2011. *Xenopus laevis* oocytes infected with multi-drug-resistant bacteria: implications for electrical recordings. J Gen Physiol 138:271–277. https://doi.org/10.1085/jgp.201110661.
196. Faulde M, Spiesberger M. 2013. Role of the moth fly *Clogmia albipunctata* (Diptera: Psychodinae) as a mechanical vector of bacterial pathogens in German hospitals. J Hosp Infect 83:51–60. https://doi.org/10.1016/j.jhin.2012.09.019.
197. Gandotra S, Kumar A, Naga K, Bhuyan PM, Gogoi DK, Sharma K, Subramanian S. 2018. Bacterial community structure and diversity in the gut of the muga silkworm, *Antheraea assamensis* (Lepidoptera: Saturniidae), from India. Insect Mol Biol 27:603–619. https://doi.org/10.1111/imb.12495.
198. Jimenez SI, Carroll C, Babcock T, Derstine N, Hadwin A, Moore M, Gries G. 2017. Yeasts harbored by Vespine wasps in the pacific northwest. Environ Entomol 46:217–225. https://doi.org/10.1093/ee/nvw173.
199. Moraes AP, Videira SS, Bittencourt VR, Bittencourt AJ. 2014. Antifungal activity of *Stenotrophomonas maltophilia* in *Stomoxys calcitrans* larvae. Rev Bras Parasitol Vet 23:194–199. https://doi.org/10.1590/s1984-29612014037.
200. Morales-Jiménez J, Zúñiga G, Ramírez-Saad HC, Hernández-Rodríguez C. 2012. Gut-associated bacteria throughout the life cycle of the bark beetle *Dendroctonus rhizophagus* Thomas and Bright (Curculionidae: Scolytinae) and their cellulolytic activities. Microb Ecol 64:268–278. https://doi.org/10.1007/s00248-011-9999-0.
201. Ozdal M, Ozdal OG, Algur OF. 2016. Isolation and characterization of α-endosulfan degrading bacteria from the microflora of cockroaches. Pol J Microbiol 65:63–68. https://doi.org/10.5604/17331331.1197325.
202. Pradeep Kumar R, John A, Kumar P, Dinesh Babu KV, Evans DA. 2018. Larvicidal efficacy of adiantobischrysene from *Adiantum latifolium* against *Oryctes rhinoceros* through disrupting metamorphosis and impeding microbial mediated digestion. Pest Manag Sci 74:1821–1828. https://doi.org/10.1002/ps.4880.
203. Qu F, Chen Q, Ding Y, Liu Z, Zhao Y, Zhang X, Liu Z, Chen J. 2018. Isolation of a feather-degrading strain of bacterium from spider gut and the purification and identification of its three key enzymes. Mol Biol Rep 45:1681–1689. https://doi.org/10.1007/s11033-018-4311-8.
204. Sevim A, Gökçe C, Erbaş Z, Özkan F. 2012. Bacteria from *Ips sexdentatus* (Coleoptera: Curculionidae) and their biocontrol potential. J Basic Microbiol 52:695–704. https://doi.org/10.1002/jobm.201100564.
205. Yadav KK, Bora A, Datta S, Chandel K, Gogoi HK, Prasad GBKS, Veer V. 2015. Molecular characterization of midgut microbiota of *Aedes albopictus* and *Aedes aegypti* from Arunachal Pradesh, India. Parasit Vectors 8:641. https://doi.org/10.1186/s13071-015-1252-0.
206. León-Palmero E, Joglar V, Álvarez PA, Martín-Platero A, Llamas I, Reche I. 2018. Diversity and antimicrobial potential in sea anemone and holothurian microbiomes. PLoS One 13:e0196178. https://doi.org/10.1371/journal.pone.0196178.

207. Reina JC, Torres M, Llamas I. 2019. *Stenotrophomonas maltophilia* AHL-degrading strains isolated from marine invertebrate microbiota attenuate the virulence of *Pectobacterium carotovorum* and *Vibrio coralliilyticus*. Mar Biotechnol (NY) 21:276–290. https://doi.org/10.1007/s10126-019-09879-w.
208. Fierst JL, Murdock DA, Thanthiriwatte C, Willis JH, Phillips PC. 2017. Metagenome-assembled draft genome sequence of a novel microbial *Stenotrophomonas maltophilia* strain isolated from *Caenorhabditis remanei* tissue. Genome Announc 5:e01646-16. https://doi.org/10.1128/genomeA.01646-16.
209. White CV, Darby BJ, Breeden RJ, Herman MA. 2016. A *Stenotrophomonas maltophilia* strain evades a major *Caenorhabditis elegans* defense pathway. Infect Immun 84:524–536. https://doi.org/10.1128/IAI.00711-15.
210. Wu X-Q, Yuan W-M, Tian X-J, Fan B, Fang X, Ye J-R, Ding X-L. 2013. Specific and functional diversity of endophytic bacteria from pine wood nematode *Bursaphelenchus xylophilus* with different virulence. Int J Biol Sci 9:34–44. https://doi.org/10.7150/ijbs.5071.
211. Zhao BG, Tao J, Ju YW, Wang PK, Ye JL. 2011. The role of wood-inhabiting bacteria in pine wilt disease. J Nematol 43:129–134.
212. Cateau E, Maisonneuve E, Peguilhan S, Quellard N, Hechard Y, Rodier M-H. 2014. *Stenotrophomonas maltophilia* and *Vermamoeba vermiformis* relationships: bacterial multiplication and protection in amoebal-derived structures. Res Microbiol 165:847–851. https://doi.org/10.1016/j.resmic.2014.10.004.
213. Corsaro D, Müller K-D, Michel R. 2013. Molecular characterization and ultrastructure of a new amoeba endoparasite belonging to the *Stenotrophomonas maltophilia* complex. Exp Parasitol 133:383–390. https://doi.org/10.1016/j.exppara.2012.12.016.
214. Denet E, Coupat-Goutaland B, Nazaret S, Pélandakis M, Favre-Bonté S. 2017. Diversity of free-living amoebae in soils and their associated human opportunistic bacteria. Parasitol Res 116:3151–3162. https://doi.org/10.1007/s00436-017-5632-6.
215. Denet E, Vasselon V, Burdin B, Nazaret S, Favre-Bonté S. 2018. Survival and growth of *Stenotrophomonas maltophilia* in free-living amoebae (FLA) and bacterial virulence properties. PLoS One 13:e0192308. https://doi.org/10.1371/journal.pone.0192308.
216. Pagnier I, Valles C, Raoult D, La Scola B. 2015. Isolation of *Vermamoeba vermiformis* and associated bacteria in hospital water. Microb Pathog 80:14–20. https://doi.org/10.1016/j.micpath.2015.02.006.
217. Muchesa P, Leifels M, Jurzik L, Hoorzook KB, Barnard TG, Bartie C. 2017. Coexistence of free-living amoebae and bacteria in selected South African hospital water distribution systems. Parasitol Res 116:155–165. https://doi.org/10.1007/s00436-016-5271-3.
218. Cha YK, Kim JS, Park SY, Oh JY, Kwon JH. 2016. Computed tomography findings of community-acquired *Stenotrophomonas maltophilia* pneumonia in an immunocompetent patient: a case report. Korean J Radiol 17:961–964. https://doi.org/10.3348/kjr.2016.17.6.961.
219. Goncalves-Vidigal P, Grosse-Onnebrink J, Mellies U, Buer J, Rath P-M, Steinmann J. 2011. *Stenotrophomonas maltophilia* in cystic fibrosis: improved detection by the use of selective agar and evaluation of antimicrobial resistance. J Cyst Fibros 10:422–427. https://doi.org/10.1016/j.jcf.2011.06.010.
220. Gallah S, Benzerara Y, Tankovic J, Woerther P-L, Bensekri H, Mainardi J-L, Arlet G, Vimont S, Garnier M. 2018. β LACTA test performance for detection of extended-spectrum β-lactamase-producing Gram-negative bacilli directly on bronchial aspirates samples: a validation study. Clin Microbiol Infect 24:402–408. https://doi.org/10.1016/j.cmi.2017.07.030.
221. Gerceker D, Karasartova D, Elyürek E, Barkar S, Kiyan M, Özsan TM, Calgin MK, Sahin F. 2009. A new, simple, rapid test for detection of DNase activity of microorganisms: DNase tube test. J Gen Appl Microbiol 55:291–294. https://doi.org/10.2323/jgam.55.291.
222. Neela V, Thomas R, Rankouhi SZR, Karunanidhi A, Shueh CS, Hamat RA, van Belkum A. 2012. Modified DNase tube test to detect DNase activity in *Stenotrophomonas maltophilia*. J Med Microbiol 61:1792–1794. https://doi.org/10.1099/jmm.0.049403-0.
223. Peräneva L, Fogarty CL, Pussinen PJ, Forsblom C, Groop P-H, Lehto M. 2013. Systemic exposure to pseudomonal bacteria: a potential link between type 1 diabetes and chronic inflammation. Acta Diabetol 50:351–361. https://doi.org/10.1007/s00592-012-0421-2.
224. Grosse-Onnebrink J, Stehling F, Tschiedel E, Olivier M, Mellies U, Schmidt R, Buer J, Rath P-M, Steinmann J. 2017. Bacteraemia and fungaemia in cystic fibrosis patients with febrile pulmonary exacerbation: a prospective observational study. BMC Pulm Med 17:96. https://doi.org/10.1186/s12890-017-0440-4.
225. Fraser TA, Bell MG, Harris PNA, Bell SC, Bergh H, Nguyen T-K, Kidd TJ, Nimmo GR, Sarovich DS, Price EP. 2019. Quantitative real-time PCR assay for the rapid identification of the intrinsically multidrug-resistant bacterial pathogen *Stenotrophomonas maltophilia*. Microb Genom 5:e000307. https://doi.org/10.1099/mgen.0.000307.
226. Rocchetti TT, Silbert S, Gostnell A, Kubasek C, Jerris R, Vong J, Widen R. 2018. Rapid detection of four non-fermenting Gram-negative bacteria directly from cystic fibrosis patient's respiratory samples on the BD MAX system. Pract Lab Med 12:e00102. https://doi.org/10.1016/j.plabm.2018.e00102.
227. Minogue E, Tuite NL, Smith CJ, Reddington K, Barry T. 2015. A rapid culture independent methodology to quantitatively detect and identify common human bacterial pathogens associated with contaminated high purity water. BMC Biotechnol 15:6. https://doi.org/10.1186/s12896-015-0124-1.
228. Vergara A, Boutal H, Ceccato A, López M, Cruells A, Bueno-Freire L, Moreno-Morales J, Puig de la Bellacasa J, Castro P, Torres A, Marco F, Casals-Pascual C, Vila J. 2020. Assessment of a loop-mediated isothermal amplification (LAMP) assay for the rapid detection of pathogenic bacteria from respiratory samples in patients with hospital-acquired pneumonia. Microorganisms 8:103. https://doi.org/10.3390/microorganisms8010103.
229. Cao J, Gao S, Chen J, Zhu B, Min R, Wang P. 2018. The preparation and clinical application of diagnostic DNA microarray for the detection of pathogens in intracranial bacterial and fungal infections. Exp Ther Med 16:1304–1310. https://doi.org/10.3892/etm.2018.6312.
230. Hansen N, Rasmussen AKI, Fiandaca MJ, Kragh KN, Bjarnsholt T, Høiby N, Stender H, Guardabassi L. 2014. Rapid identification of *Stenotrophomonas maltophilia* by peptide nucleic acid fluorescence *in situ* hybridization. New Microbes New Infect 2:79–81. https://doi.org/10.1002/nmi2.38.
231. Ko ER, Philipson CW, Burke TW, Cer RZ, Bishop-Lilly KA, Voegtly LJ, Tsalik EL, Woods CW, Clark DV, Schully KL. 2019. Direct-from-blood RNA sequencing identifies the cause of post-bronchoscopy fever. BMC Infect Dis 19:905. https://doi.org/10.1186/s12879-019-4462-9.
232. Gherardi G, Creti R, Pompilio A, Di Bonaventura G. 2015. An overview of various typing methods for clinical epidemiology of the emerging pathogen *Stenotrophomonas maltophilia*. Diagn Microbiol Infect Dis 81:219–226. https://doi.org/10.1016/j.diagmicrobio.2014.11.005.
233. Camargo JF, Ahmed AA, Lindner MS, Morris MI, Anjan S, Anderson AD, Prado CE, Dalai SC, Martinez OV, Komanduri KV. 2019. Next-generation sequencing of microbial cell-free DNA for rapid noninvasive diagnosis of infectious diseases in immunocompromised hosts. F1000Res 8:1194. https://doi.org/10.12688/f1000research.19766.4.
234. Gonçalves Vidigal P, Schmidt D, Stehling F, Mellies U, Steinmann E, Buer J, Rath P-M, Steinmann J. 2013. Development of a quantitative immunofluorescence assay for detection of *Stenotrophomonas maltophilia* antibodies in patients with cystic fibrosis. J Cyst Fibros 12:651–654. https://doi.org/10.1016/j.jcf.2013.04.011.
235. Wang H, Drake SK, Yong C, Gucek M, Lyes MA, Rosenberg AZ, Soderblom E, Arthur Moseley M, Dekker JP, Suffredini AF. 2017. A genoproteomic approach to detect peptide markers of bacterial respiratory pathogens. Clin Chem 63:1398–1408. https://doi.org/10.1373/clinchem.2016.269647.
236. Shestivska V, Dryahina K, Nunvář J, Sovová K, Elhottová D, Nemec A, Smith D, Španěl P. 2015. Quantitative analysis of volatile metabolites released *in vitro* by bacteria of the genus *Stenotrophomonas* for identification of breath biomarkers of respiratory infection in cystic fibrosis. J Breath Res 9:e027104. https://doi.org/10.1088/1752-7155/9/2/027104.
237. Dryahina K, Sovová K, Nemec A, Španěl P. 2016. Differentiation of pulmonary bacterial pathogens in cystic fibrosis by volatile metabolites emitted by their *in vitro* cultures: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia* and the *Burkholderia cepacia* complex. J Breath Res 10:037102. https://doi.org/10.1088/1752-7155/10/3/037102.
238. Nizio KD, Perrault KA, Troobnikoff AN, Ueland M, Shoma S, Iredell JR, Middleton PG, Forbes SL. 2016. *In vitro* volatile organic compound profiling using GC$\times$GC-TOFMS to differentiate bacteria associated with lung infections: a proof-of-concept study. J Breath Res 10:026008. https://doi.org/10.1088/1752-7155/10/2/026008.
239. Zhao S, Wang L, Cao S, Liu J, Zhang Z, Li L, Chen F, Wu Q. 2020. A preliminary study on the homology analysis of clinical *Stenotrophomonas maltophilia* isolates based on fatty acid profiles. New Microbiol 43:82–88.
240. Gautam V, Sharma M, Singhal L, Kumar S, Kaur P, Tiwari R, Ray P. 2017. MALDI-TOF mass spectrometry: an emerging tool for unequivocal identification of non-fermenting Gram-negative bacilli. Indian J Med Res 145:665–672. https://doi.org/10.4103/ijmr.IJMR_1105_15.

241. Homem de Mello de Souza HAP, Dalla-Costa LM, Vicenzi FJ, Camargo de Souza D, Riedi CA, Filho NAR, Pilonetto M. 2014. MALDI-TOF: a useful tool for laboratory identification of uncommon glucose non-fermenting Gram-negative bacteria associated with cystic fibrosis. J Med Microbiol 63:1148–1153. https://doi.org/10.1099/jmm.0.076869-0.
242. Hou T-Y, Chiang-Ni C, Teng S-H. 2019. Current status of MALDI-TOF mass spectrometry in clinical microbiology. J Food Drug Anal 27:404–414. https://doi.org/10.1016/j.jfda.2019.01.001.
243. Arroyo MA, Denys GA. 2017. Parallel evaluation of the MALDI sepsityper and verigene BC-GN assays for rapid identification of gram-negative bacilli from positive blood cutures. J Clin Microbiol 55:2708–2718. https://doi.org/10.1128/JCM.00692-17.
244. Kok J, Thomas LC, Olma T, Chen SCA, Iredell JR. 2011. Identification of bacteria in blood culture broths using matrix-assisted laser desorption-ionization Sepsityper and time of flight mass spectrometry. PLoS One 6:e23285. https://doi.org/10.1371/journal.pone.0023285.
245. Florio W, Tavanti A, Barnini S, Ghelardi E, Lupetti A. 2018. Recent advances and ongoing challenges in the diagnosis of microbial infections by MALDI-TOF mass spectrometry. Front Microbiol 9:1097. https://doi.org/10.3389/fmicb.2018.01097.
246. Gao G, Wang D, Brocenschi R, Zhi J, Mirkin MV. 2018. Toward the detection and identification of single bacteria by electrochemical collision technique. Anal Chem 90:12123–12130. https://doi.org/10.1021/acs.analchem.8b03043.
247. Adamek M, Linke B, Schwartz T. 2014. Virulence genes in clinical and environmental *Stenotrophomas maltophilia* isolates: a genome sequencing and gene expression approach. Microb Pathog 67–68:20–30. https://doi.org/10.1016/j.micpath.2014.02.001.
248. Akbar S, Rout SP, Humphreys PN. 2015. Draft genome sequence of the biofilm-forming *Stenotrophomonas maltophilia* strain 53. Genome Announc 3:e00312-15. https://doi.org/10.1128/genomea.00312-15.
249. Davenport KW, Daligault HE, Minogue TD, Broomall SM, Bruce DC, Chain PS, Coyne SR, Gibbons HS, Jaissle J, Li P-E, Rosenzweig CN, Scholz MB, Johnson SL. 2014. Complete genome sequence of *Stenotrophomonas maltophilia* type strain 810–2 (ATCC 13637). Genome Announc 2:e00974-14. https://doi.org/10.1128/genomeA.00974-14.
250. Patil PP, Midha S, Kumar S, Patil PB. 2016. Genome sequence of type strains of genus *Stenotrophomonas*. Front Microbiol 7:309. https://doi.org/10.3389/fmicb.2016.00309.
251. Crossman LC, Gould VC, Dow JM, Vernikos GS, Okazaki A, Sebaihia M, Saunders D, Arrowsmith C, Carver T, Peters N, Adlem E, Kerhornou A, Lord A, Murphy L, Seeger K, Squares R, Rutter S, Quail MA, Rajandream MA, Harris D, Churcher C, Bentley SD, Parkhill J, Thomson NR, Avison MB. 2008. The complete genome, comparative and functional analysis of *Stenotrophomonas maltophilia* reveals an organism heavily shielded by drug resistance determinants. Genome Biol 9:R74. https://doi.org/10.1186/gb-2008-9-4-r74.
252. Lira F, Hernández A, Belda E, Sánchez MB, Moya A, Silva FJ, Martínez JL. 2012. Whole-genome sequence of *Stenotrophomonas maltophilia* D457, a clinical isolate and a model strain. J Bacteriol 194:3563–3564. https://doi.org/10.1128/JB.00602-12.
253. Patil PP, Kumar S, Midha S, Gautam V, Patil PB. 2018. Taxonogenomics reveal multiple novel genomospecies associated with clinical isolates of *Stenotrophomonas maltophilia*. Microb Genom 4:e000207. https://doi.org/10.1099/mgen.0.000207.
254. Alavi P, Starcher MR, Thallinger GG, Zachow C, Müller H, Berg G. 2014. *Stenotrophomonas* comparative genomics reveals genes and functions that differentiate beneficial and pathogenic bacteria. BMC Genomics 15:482. https://doi.org/10.1186/1471-2164-15-482.
255. Adamek M, Overhage J, Bathe S, Winter J, Fischer R, Schwartz T. 2011. Genotyping of environmental and clinical *Stenotrophomonas maltophilia* isolates and their pathogenic potential. PLoS One 6:e27615. https://doi.org/10.1371/journal.pone.0027615.
256. Bostanghadiri N, Ghalavand Z, Fallah F, Yadegar A, Ardebili A, Tarashi S, Pournajaf A, Mardaneh J, Shams S, Hashemi A. 2019. Characterization of phenotypic and genotypic diversity of *Stenotrophomonas maltophilia* strains isolated from selected hospitals in Iran. Front Microbiol 10:1191. https://doi.org/10.3389/fmicb.2019.01191.
257. Svensson-Stadler LA, Mihaylova SA, Moore ERB. 2012. *Stenotrophomonas* interspecies differentiation and identification by *gyrB* sequence analysis. FEMS Microbiol Lett 327:15–24. https://doi.org/10.1111/j.1574-6968.2011.02452.x.
258. Madi H, Lukić J, Vasiljević Z, Biočanin M, Kojić M, Jovčić B, Lozo J. 2016. Genotypic and phenotypic characterization of *Stenotrophomonas maltophilia* strains from a pediatric tertiary care hospital in Serbia. PLoS One 11:e0165660. https://doi.org/10.1371/journal.pone.0165660.
259. Steinmann J, Mamat U, Abda EM, Kirchhoff L, Streit WR, Schaible UE, Niemann S, Kohl TA. 2018. Analysis of phylogenetic variation of *Stenotrophomonas maltophilia* reveals human-specific branches. Front Microbiol 9:806. https://doi.org/10.3389/fmicb.2018.00806.
260. Esposito A, Pompilio A, Bettua C, Crocetta V, Giacobazzi E, Fiscarelli E, Jousson O, Di Bonaventura G. 2017. Evolution of *Stenotrophomonas maltophilia* in cystic fibrosis lung over chronic infection: a genomic and phenotypic population study. Front Microbiol 8:1590. https://doi.org/10.3389/fmicb.2017.01590.
261. Lira F, Berg G, Martínez JL. 2017. Double-face meets the bacterial world: the opportunistic pathogen *Stenotrophomonas maltophilia*. Front Microbiol 8:2190. https://doi.org/10.3389/fmicb.2017.02190.
262. Youenou B, Favre-Bonté S, Bodilis J, Brothier E, Dubost A, Muller D, Nazaret S. 2015. Comparative genomics of environmental and clinical *Stenotrophomonas maltophilia* strains with different antibiotic resistance profiles. Genome Biol Evol 7:2484–2505. https://doi.org/10.1093/gbe/evv161.
263. Yu D, Yin Z, Li B, Jin Y, Ren H, Zhou J, Zhou W, Liang L, Yue J. 2016. Gene flow, recombination, and positive selection in *Stenotrophomonas maltophilia*: mechanisms underlying the diversity of the widespread opportunistic pathogen. Genome 59:1063–1075. https://doi.org/10.1139/gen-2016-0073.
264. Paopradit P, Srinitiwarawong K, Ingviya N, Singkhamanan K, Vuddhakul V. 2017. Distribution and characterization of *Stenotrophomonas maltophilia* isolates from environmental and clinical samples in Thailand. J Hosp Infect 97:185–191. https://doi.org/10.1016/j.jhin.2017.06.006.
265. Pompilio A, Pomponio S, Crocetta V, Gherardi G, Verginelli F, Fiscarelli E, Dicuonzo G, Savini V, D'Antonio D, Di Bonaventura G. 2011. Phenotypic and genotypic characterization of *Stenotrophomonas maltophilia* isolates from patients with cystic fibrosis: genome diversity, biofilm formation, and virulence. BMC Microbiol 11:159. https://doi.org/10.1186/1471-2180-11-159.
266. Flores-Treviño S, Gutiérrez-Ferman JL, Morfín-Otero R, Rodríguez-Noriega E, Estrada-Rivadeneyra D, Rivas-Morales C, Llaca-Díaz JM, Camacho-Ortíz A, Mendoza-Olazarán S, Garza-González E. 2014. *Stenotrophomonas maltophilia* in Mexico: antimicrobial resistance, biofilm formation and clonal diversity. J Med Microbiol 63:1524–1530. https://doi.org/10.1099/jmm.0.074385-0.
267. Corlouer C, Lamy B, Desroches M, Ramos-Vivas J, Mehiri-Zghal E, Lemenand O, Delarbre J-M, Decousser J-W, Collège de Bactériologie-Virologie-Hygiène des Hôpitaux de France. 2017. *Stenotrophomonas maltophilia* healthcare-associated infections: identification of two main pathogenic genetic backgrounds. J Hosp Infect 96:183–188. https://doi.org/10.1016/j.jhin.2017.02.003.
268. Mojica MF, Rutter JD, Taracila M, Abriata LA, Fouts DE, Papp-Wallace KM, Walsh TJ, LiPuma JJ, Vila AJ, Bonomo RA. 2019. Population structure, molecular epidemiology, and β-lactamase diversity among *Stenotrophomonas maltophilia* isolates in the United States. mBio 10:e00405-19. https://doi.org/10.1128/mBio.00405-19.
269. Mercier-Darty M, Royer G, Lamy B, Charron C, Lemenand O, Gomart C, Fourreau F, Madec J-Y, Jumas-Bilak E, Decousser J-W, RESAPATH Network, the ColBVH Network. 2020. Comparative whole-genome phylogeny of animal, environmental, and human strains confirms the genogroup organization and diversity of the *Stenotrophomonas maltophilia* complex. Appl Environ Microbiol 86:e02919-19. https://doi.org/10.1128/AEM.02919-19.
270. Hauben L, Vauterin L, Moore ER, Hoste B, Swings J. 1999. Genomic diversity of the genus *Stenotrophomonas*. Int J Syst Evol Microbiol 49:1749–1760. https://doi.org/10.1099/00207713-49-4-1749.
271. Kaiser S, Biehler K, Jonas D. 2009. A *Stenotrophomonas maltophilia* multilocus sequence typing scheme for inferring population structure. J Bacteriol 191:2934–2943. https://doi.org/10.1128/JB.00892-08.
272. Güvenir M, Otlu B, Tunc E, Aktas E, Suer K. 2018. High genetic diversity among *Stenotrophomonas maltophilia* isolates from single hospital: nosocomial outbreaks or genotypic profile changes during subcultures. Malays J Med Sci 25:40–49. https://doi.org/10.21315/mjms2018.25.2.5.
273. Gröschel MI, Meehan CJ, Barilar I, Diricks M, Gonzaga A, Steglich M, Conchillo-Solé O, Scherer I-C, Mamat U, Luz CF, De Bruyne K, Utpatel C, Yero D, Gibert I, Daura X, Kampmeier S, Rahman NA, Kresken M, van der Werf TS, Alio I, Streit WR, Zhou K, Schwartz T, Rossen JWA, Farhat MR, Schaible UE, Nübel U, Rupp J, Steinmann J, Niemann S, Kohl TA. 2020. The phylogenetic landscape and nosocomial spread of the multidrug-

resistant opportunist *Stenotrophomonas maltophilia*. Nat Commun 11:2044. https://doi.org/10.1038/s41467-020-15123-0.

274. Gallagher T, Phan J, Oliver A, Chase AB, England WE, Wandro S, Hendrickson C, Riedel SF, Whiteson K. 2019. Cystic fibrosis-associated *Stenotrophomonas maltophilia* strain-specific adaptations and responses to pH. J Bacteriol 201:e00478-18. https://doi.org/10.1128/JB.00478-18.
275. Willsey GG, Eckstrom K, LaBauve AE, Hinkel LA, Schutz K, Meagher RJ, LiPuma JJ, Wargo MJ. 2019. *Stenotrophomonas maltophilia* differential gene expression in synthetic cystic fibrosis sputum reveals shared and cystic fibrosis strain-specific responses to the sputum environment. J Bacteriol 201:e00074-19. https://doi.org/10.1128/JB.00074-19.
276. Welker E, Domfeh Y, Tyagi D, Sinha S, Fisher N. 2015. Genetic manipulation of *Stenotrophomonas maltophilia*. Curr Protoc Microbiol 37:6F.2.1–-6F.2.14. https://doi.org/10.1002/9780471729259.mc06f02s37.
277. Huang Y-W, Hu R-M, Chiang Y-T, Chung T-C, Chung T-C, Yang T-C. 2011. Establishment of an arabinose-inducible system in *Stenotrophomonas maltophilia*. Folia Microbiol (Praha) 56:18–22. https://doi.org/10.1007/s12223-011-0008-2.
278. Ye X, Dong H, Huang Y-P. 2014. Highly efficient transformation of *Stenotrophomonas maltophilia* S21, an environmental isolate from soil, by electroporation. J Microbiol Methods 107:92–97. https://doi.org/10.1016/j.mimet.2014.09.010.
279. Brooke JS, Vo A, Watts P, Davis NA. 2008. Mutation of a lipopolysaccharide synthesis gene results in increased biofilm of *Stenotrophomonas maltophilia* on plastic and glass surfaces. Ann Microbiol 58:35–40. https://doi.org/10.1007/BF03179442.
280. Huang T-P, Somers EB, Wong ACL. 2006. Differential biofilm formation and motility associated with lipopolysaccharide/exopolysaccharide coupled biosynthetic genes in *Stenotrophomonas maltophilia*. J Bacteriol 188:3116–3120. https://doi.org/10.1128/JB.188.8.3116-3120.2006.
281. Zgair AK, Al-Adressi AMH. 2013. *Stenotrophomonas maltophilia* fimbrin stimulates mouse bladder innate immune response. Eur J Clin Microbiol Infect Dis 32:139–146. https://doi.org/10.1007/s10096-012-1729-0.
282. An S-Q, Caly DL, McCarthy Y, Murdoch SL, Ward J, Febrer M, Dow JM, Ryan RP. 2014. Novel cyclic di-GMP effectors of the YajQ protein family control bacterial virulence. PLoS Pathog 10:e1004429. https://doi.org/10.1371/journal.ppat.1004429.
283. Ioannidis O, Papaziogas B, Tsiaousis P, Paraskevas G, Giamarellos-Bourboulis EJ, Koutelidakis I. 2014. Effect of moxifloxacin on survival, lipid peroxidation and inflammation in immunosuppressed rats with soft tissue infection cuased by *Stenotrophomonas maltophilia*. Microbiol Immunol 58:96–102. https://doi.org/10.1111/1348-0421.12124.
284. Thomas R, Hamat RA, Neela V. 2013. *Stenotrophomonas maltophilia*: pathogenesis model using *Caenorhabditis elegans*. J Med Microbiol 62:1777–1779. https://doi.org/10.1099/jmm.0.063230-0.
285. Ferrer-Navarro M, Planell R, Yero D, Mongiardini E, Torrent G, Huedo P, Martínez P, Roher N, Mackenzie S, Gibert I, Daura X. 2013. Abundance of the quorum-sensing factor Ax21 in four strains of *Stenotrophomonas maltophilia* correlates with mortality rate in a new zebrafish model of infection. PLoS One 8:e67207. https://doi.org/10.1371/journal.pone.0067207.
286. Roscetto E, Angrisano T, Costa V, Casalino M, Förstner KU, Sharma CM, Di Nocera PP, De Gregorio E. 2012. Functional characterization of the RNA chaperone Hfq in the opportunistic human pathogen *Stenotrophomonas maltophilia*. J Bacteriol 194:5864–5874. https://doi.org/10.1128/JB.00746-12.
287. Thomas R, Hamat RA, Neela V. 2014. Extracellular enzyme profiling of *Stenotrophomonas maltophilia* clinical isolates. Virulence 5:326–330. https://doi.org/10.4161/viru.27724.
288. MacDonald LC, Berger BW. 2014. A polysaccharide lyase from *Stenotrophomonas maltophilia* with a unique, pH-regulated substrate specificity. J Biol Chem 289:312–325. https://doi.org/10.1074/jbc.M113.489195.
289. Jair H-W, Lu H-F, Huang Y-W, Pan S-Y, Lin I-L, Huang H-H, Yang T-C. 2019. Roles of the two-MnSOD system of *Stenotrophomonas maltophilia* in the alleviation of superoxide stress. Int J Mol Sci 20:1770. https://doi.org/10.3390/ijms20071770.
290. Li L-H, Shih Y-L, Huang J-Y, Wu C-J, Huang Y-W, Huang H-H, Tsai Y-C, Yang T-C. 2020. Protection from hydrogen peroxide stress relies mainly on AhpCF and KatA2 in *Stenotrophomonas maltophilia*. J Biomed Sci 27:37. https://doi.org/10.1186/s12929-020-00631-4.
291. Chang YT, Lin CY, Chen YH, Hsueh PR. 2015. Update on infections caused by *Stenotrophomonas maltophilia* with particular attention to resistance mechanisms and therapeutic options. Front Microbiol 6:893. https://doi.org/10.3389/fmicb.2015.00893.
292. Blanco P, Corona F, Martínez JL. 2019. Involvement of the RND efflux pump transporter SmeH in the acquisition of resistance to ceftazidime in *Stenotrophomonas maltophilia*. Sci Rep 9:4917. https://doi.org/10.1038/s41598-019-41308-9.
293. Blanco P, Corona F, Martinez JL. 2019. Mechanisms and phenotypic consequences of acquisition of tigecycline resistance by *Stenotrophomonas maltophilia*. J Antimicrob Chemother 74:3221–3230. https://doi.org/10.1093/jac/dkz326.
294. García-León G, Salgado F, Oliveros JC, Sánchez MB, Martínez JL. 2014. Interplay between intrinsic and acquired resistance to quinolones in *Stenotrophomonas maltophilia*. Environ Microbiol 16:1282–1296. https://doi.org/10.1111/1462-2920.12408.
295. García-León G, Sánchez MB, Martínez JL. 2012. The inactivation of intrinsic antibiotic resistance determinants widens the mutant selection window for quinolones in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 56:6397–6399. https://doi.org/10.1128/AAC.01558-12.
296. Calvopiña K, Dulyayangkul P, Heesom KJ, Avison MB. 2020. TonB-dependent uptake of β-lactam antibiotics in the opportunistic human pathogen *Stenotrophomonas maltophilia*. Mol Microbiol 113:492–503. https://doi.org/10.1111/mmi.14434.
297. Huang Y-W, Hu R-M, Lin C-W, Chung T-C, Yang T-C. 2012. NagZ-dependent and NagZ-independent mechanisms for β-lactamase expression in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 56:1936–1941. https://doi.org/10.1128/AAC.05645-11.
298. Lin C-W, Lin H-C, Huang Y-W, Chung T-C, Yang T-C. 2011. Inactivation of *mrcA* gene derepresses the basal-level expression of L1 and L2 β-lactamases in *Stenotrophomonas maltophilia*. J Antimicrob Chemother 66:2033–2037. https://doi.org/10.1093/jac/dkr276.
299. Huang Y-W, Wu C-J, Hu R-M, Lin Y-T, Yang T-C. 2015. Interplay among membrane-bound lytic transglycosylase D1, the CreBC two-component regulatory system, the AmpNG-AmpD$_I$-NagZ-AmpR regulatory circuit, and L1/L2 β-lactamase expression in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 59:6866–6872. https://doi.org/10.1128/AAC.05179-14.
300. Talfan A, Mounsey O, Charman M, Townsend E, Avison MB. 2013. Involvement of mutation in *ampD* I, *mrcA*, and at least one additional gene in β-lactamase hyperproduction in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 57:5486–5491. https://doi.org/10.1128/AAC.01446-13.
301. Van Oudenhove L, De Vriendt K, Van Beeumen J, Mercuri PS, Devreese B. 2012. Differential proteomic analysis of the response of *Stenotrophomonas maltophilia* to imipenem. Appl Microbiol Biotechnol 95:717–733. https://doi.org/10.1007/s00253-012-4167-0.
302. Sánchez MB. 2015. Antibiotic resistance in the opportunistic pathogen *Stenotrophomonas maltophilia*. Front Microbiol 6:658. https://doi.org/10.3389/fmicb.2015.00658.
303. Tada T, Miyoshi-Akiyama T, Dahal RK, Mishra SK, Shimada K, Ohara H, Kirikae T, Pokhrel BM. 2014. Identification of a novel 6'-*N*-aminoglycoside acetyltransferase, AAC(6')-Iak, from a multidrug-resistant clinical isolate of *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 58:6324–6327. https://doi.org/10.1128/AAC.03354-14.
304. Huang H-H, Lin Y-T, Chen P-Y, Li L-H, Ning H-C, Yang T-C. 2018. ClpA and HtpX proteases are involved in intrinsic aminoglycoside resistance of *Stenotrophomonas maltophilia* and are potential aminoglycoside adjuvant targets. Antimicrob Agents Chemother 62:e00554-18. https://doi.org/10.1128/AAC.00554-18.
305. Bernardini A, Martínez JL. 2017. Genome-wide analysis shows that RNase G plays a global role in the stability of mRNAs in *Stenotrophomonas maltophilia*. Sci Rep 7:16016. https://doi.org/10.1038/s41598-017-16091-0.
306. Bernardini A, Corona F, Dias R, Sánchez MB, Martínez JL. 2015. The inactivation of RNase G reduces the *Stenotrophomonas maltophilia* susceptibility to quinolones by triggering the heat shock response. Front Microbiol 6:1068. https://doi.org/10.3389/fmicb.2015.01068.
307. Huang Y-W, Hu R-M, Lin Y-T, Huang H-H, Yang T-C. 2015. The contribution of class 1 integron to antimicrobial resistance in *Stenotrophomonas maltophilia*. Microb Drug Resist 21:90–96. https://doi.org/10.1089/mdr.2014.0072.
308. Zhao Y, Niu W, Sun Y, Hao H, Yu D, Xu G, Shang X, Tang X, Lu S, Yue J, Li Y. 2015. Identification and characterization of a serious multidrug resistant *Stenotrophomonas maltophilia* strain in China. Biomed Res Int 2015:580240. https://doi.org/10.1155/2015/580240.
309. Hu L-F, Chang X, Ye Y, Wang Z-X, Shao Y-B, Shi W, Li X, Li J-B. 2011. *Stenotrophomonas maltophilia* resistance to trimethoprim/sulfamethoxazole mediated by acquisition of *sul* and *dfrA* genes in a plasmid-mediated

class 1 integron. Int J Antimicrob Agents 37:230–234. https://doi.org/10.1016/j.ijantimicag.2010.10.025.
310. Chung H-S, Kim K, Hong SS, Hong SG, Lee K, Chong Y. 2015. The *sul1* gene in *Stenotrophomonas maltophilia* with high-level resistance to trimethoprim/sulfamethoxazole. Ann Lab Med 35:246–249. https://doi.org/10.3343/alm.2015.35.2.246.
311. Lin Y-T, Huang Y-W, Liou R-S, Chang Y-C, Yang T-C. 2014. MacABCsm, an ABC-type tripartite efflux pump of *Stenotrophomonas maltophilia* involved in drug resistance, oxidative and envelope stress tolerances and biofilm formation. J Antimicrob Chemother 69:3221–3226. https://doi.org/10.1093/jac/dku317.
312. Huang Y-W, Hu R-M, Yang T-C. 2013. Role of the *pcm-tolCsm* operon in the multidrug resistance of *Stenotrophomonas maltophilia*. J Antimicrob Chemother 68:1987–1993. https://doi.org/10.1093/jac/dkt148.
313. Li L-H, Zhang M-S, Wu C-J, Lin Y-T, Yang T-C. 2019. Overexpression of SmeGH contributes to the acquired MDR of *Stenotrophomonas maltophilia*. J Antimicrob Chemother 74:2225–2229. https://doi.org/10.1093/jac/dkz200.
314. Lin C-W, Huang Y-W, Hu R-M, Yang T-C. 2014. SmeOP-TolCSm efflux pump contributes to the multidrug resistance of *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 58:2405–2408. https://doi.org/10.1128/AAC.01974-13.
315. Al-Hamad A, Burnie J, Upton M. 2011. Enhancement of antibiotic susceptibility of *Stenotrophomonas maltophilia* using a polyclonal antibody developed against an ABC multidrug efflux pump. Can J Microbiol 57:820–828. https://doi.org/10.1139/w11-076.
316. Huang Y-W, Hu R-M, Chu F-Y, Lin H-R, Yang T-C. 2013. Characterization of a major facilitator superfamily (MFS) tripartite efflux pump EmrCABsm from *Stenotrophomonas maltophilia*. J Antimicrob Chemother 68:2498–2505. https://doi.org/10.1093/jac/dkt250.
317. Dulyayangkul P, Charoenlap N, Srijaruskul K, Mongkolsuk S, Vattanaviboon P. 2016. Major facilitator superfamily MfsA contributes to multidrug resistance in emerging nosocomial pathogen *Stenotrophomonas maltophilia*. J Antimicrob Chemother 71:2990–2991. https://doi.org/10.1093/jac/dkw233.
318. Srijaruskul K, Charoenlap N, Namchaiw P, Chattrakarn S, Giengkam S, Mongkolsuk S, Vattanaviboon P. 2015. Regulation by SoxR of *mfsA*, which encodes a major facilitator protein involved in paraquat resistance in *Stenotrophomonas maltophilia*. PLoS One 10:e0123699. https://doi.org/10.1371/journal.pone.0123699.
319. Vattanaviboon P, Dulyayangkul P, Mongkolsuk S, Charoenlap N. 2018. Overexpression of *Stenotrophomonas maltophilia* major facilitator superfamily protein MfsA increases resistance to fluoroquinolone antibiotics. J Antimicrob Chemother 73:1263–1266. https://doi.org/10.1093/jac/dky024.
320. Cho HH, Sung JY, Kwon CK, Koo SH. 2012. Expression of Sme efflux pumps and multilocus sequence typing in clinical isolates of *Stenotrophomonas maltophilia*. Ann Lab Med 32:38–43. https://doi.org/10.3343/alm.2012.32.1.38.
321. Hernández A, Ruiz FM, Romero A, Martínez JL. 2011. The binding of triclosan to SmeT, the repressor of the multidrug efflux pump SmeDEF, induces antibiotic resistance in *Stenotrophomonas maltophilia*. PLoS Pathog 7:e1002103. https://doi.org/10.1371/journal.ppat.1002103.
322. García-León G, Hernández A, Hernando-Amado S, Alavi P, Berg G, Martínez JL. 2014. A function of SmeDEF, the major quinolone resistance determinant of *Stenotrophomonas maltophilia*, is the colonization of plant roots. Appl Environ Microbiol 80:4559–4565. https://doi.org/10.1128/AEM.01058-14.
323. Sánchez MB, Martínez JL. 2015. The efflux pump SmeDEF contributes to trimethoprim-sulfamethoxazole resistance in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 59:4347–4348. https://doi.org/10.1128/AAC.00714-15.
324. Pak TR, Altman DR, Attie O, Sebra R, Hamula CL, Lewis M, Deikus G, Newman LC, Fang G, Hand J, Patel G, Wallach F, Schadt EE, Huprikar S, van Bakel H, Kasarskis A, Bashir A. 2015. Whole-genome sequencing identifies emergence of a quinolone resistance mutation in a case of *Stenotrophomonas maltophilia* bacteremia. Antimicrob Agents Chemother 59:7117–7120. https://doi.org/10.1128/AAC.01723-15.
325. Huang Y-W, Lin C-W, Ning H-C, Lin Y-T, Chang Y-C, Yang T-C. 2017. Overexpression of SmeDEF efflux pump decreases aminoglycoside resistance in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 61:e02685-16. https://doi.org/10.1128/AAC.02685-16.
326. Chong SY, Lee K, Chung H-S, Hong SG, Suh Y, Chong Y. 2017. Levofloxacin efflux and *smeD* in clinical isolates of *Stenotrophomonas maltophilia*. Microb Drug Resist 23:163–168. https://doi.org/10.1089/mdr.2015.0228.
327. Gould VC, Okazaki A, Avison MB. 2013. Coordinate hyperproduction of SmeZ and SmeJK efflux pumps extends drug resistance in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 57:655–657. https://doi.org/10.1128/AAC.01020-12.
328. Huang Y-W, Liou R-S, Lin Y-T, Huang H-H, Yang T-C. 2014. A linkage between SmeIJK efflux pump, cell envelope integrity, and σ^E-mediated envelope stress response in *Stenotrophomonas maltophilia*. PLoS One 9:e111784. https://doi.org/10.1371/journal.pone.0111784.
329. Chen C-H, Huang C-C, Chung T-C, Hu R-M, Huang Y-W, Yang T-C. 2011. Contribution of resistance-nodulation-division efflux pump operon *smeU1-V-W-U2-X* to multidrug resistance of *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 55:5826–5833. https://doi.org/10.1128/AAC.00317-11.
330. Blanco P, Corona F, Sánchez MB, Martínez JL. 2017. Vitamin K_3 induces the expression of the *Stenotrophomonas maltophilia* SmeVWX multidrug efflux pump. Antimicrob Agents Chemother 61:e02453-16. https://doi.org/10.1128/AAC.02453-16.
331. Wu C-J, Lu H-F, Lin Y-T, Zhang M-S, Li L-H, Yang T-C. 2019. Substantial contribution of SmeDEF, SmeVWX, SmQnr, and heat shock response to fluoroquinolone resistance in clinical isolates of *Stenotrophomonas maltophilia*. Front Microbiol 10:822. https://doi.org/10.3389/fmicb.2019.00822.
332. Lin Y-T, Huang Y-W, Chen S-J, Chang C-W, Yang T-C. 2015. The SmeYZ efflux pump of *Stenotrophomonas maltophilia* contributes to drug resistance, virulence-related characteristics, and virulence in mice. Antimicrob Agents Chemother 59:4067–4073. https://doi.org/10.1128/AAC.00372-15.
333. Calvopiña K, Dulyayangkul P, Avison MB. 2019. Mutations in ribosomal protein RplA or treatment with ribosomal acting antibiotics activates production of aminoglycoside efflux pump SmeYZ in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 64:e01524-19. https://doi.org/10.1128/AAC.01524-19.
334. Wu C-J, Huang Y-W, Lin Y-T, Ning H-C, Yang T-C. 2016. Inactivation of SmeSyRy two-component regulatory system inversely regulates the expression of SmeYZ and SmeDEF efflux pumps in *Stenotrophomonas maltophilia*. PLoS One 11:e0160943. https://doi.org/10.1371/journal.pone.0160943.
335. Liu M-C, Tsai Y-L, Huang Y-W, Chen H-Y, Hsueh P-R, Lai S-Y, Chen L-C, Chou Y-H, Lin W-Y, Liaw S-J. 2016. *Stenotrophomonas maltophilia* PhoP, a two-component response regulator, involved in antimicrobial susceptibilities. PLoS One 11:e0153753. https://doi.org/10.1371/journal.pone.0153753.
336. Hu R-M, Liao S-T, Huang C-C, Huang Y-W, Yang T-C. 2012. An inducible fusaric acid tripartite efflux pump contributes to the fusaric acid resistance in *Stenotrophomonas maltophilia*. PLoS One 7:e51053. https://doi.org/10.1371/journal.pone.0051053.
337. Ni W, Li Y, Guan J, Zhao J, Cui J, Wang R, Liu Y. 2016. Effects of efflux pump inhibitors on colistin resistance in multidrug-resistant Gram-negative bacteria. Antimicrob Agents Chemother 60:3215–3218. https://doi.org/10.1128/AAC.00248-16.
338. Blanco P, Corona F, Martínez JL. 2018. Biolog phenotype microarray is a tool for the identification of multidrug resistance efflux pump inducers. Antimicrob Agents Chemother 62:e01263-18. https://doi.org/10.1128/AAC.01263-18.
339. Sánchez MB, Decorosi F, Viti C, Oggioni MR, Martínez JL, Hernández A. 2015. Predictive studies suggest that the risk for the selection of antibiotic resistance by biocides is likely low in *Stenotrophomonas maltophilia*. PLoS One 10:e0132816. https://doi.org/10.1371/journal.pone.0132816.
340. Gallo SW, Figueiredo TP, Bessa MC, Pagnussatti VE, Ferreira CAS, Oliveira SD. 2016. Isolation and characterization of *Stenotrophomonas maltophilia* isolates from a Brazilian hospital. Microb Drug Resist 22:688–695. https://doi.org/10.1089/mdr.2015.0306.
341. Zhao S, Yang L, Liu H, Gao F. 2017. *Stenotrophomonas maltophilia* in a university hospital of traditional Chinese medicine: molecular epidemiology and antimicrobial resistance. J Hosp Infect 96:286–289. https://doi.org/10.1016/j.jhin.2017.04.001.
342. Hu L-F, Xu X-H, Li H-R, Gao L-P, Chen X, Sun N, Liu Y-Y, Ying H-F, Li J-B. 2018. Surveillance of antimicrobial susceptibility patterns among *Stenotrophomonas maltophilia* isolated in China during the 10-year period of 2005–2014. J Chemother 30:25–30. https://doi.org/10.1080/1120009X.2017.1378834.
343. Kim SY, Shin SY, Rhee J-Y, Ko KS. 2017. Imipenem-resistant Gram-negative bacterial isolates carried by persons upon medical examination in Korea. J Microbiol 55:612–618. https://doi.org/10.1007/s12275-017-6555-8.
344. Bhavana MV, Joshi S, Adhikary R, Beena HB. 2017. Antibiotic susceptibility pattern of *Burkholderia cepacia* complex and *Stenotrophomonas maltophilia*: a 5-year analysis. Indian J Med Microbiol 35:318–319. https://doi.org/10.4103/ijmm.IJMM_16_236.

345. Gajdács M, Urbán E. 2019. Prevalence and antibiotic resistance of *Stenotrophomonas maltophilia* in respiratory tract samples: a 10-year epidemiological snapshot. Health Serv Res Manag Epidemiol 6:2333392819870774. https://doi.org/10.1177/2333392819870774.
346. Sedigh Ebrahim-Saraie H, Heidari H, Soltani B, Mardaneh J, Motamedifar M. 2019. Prevalence of antibiotic resistance and integrons, *sul* and *Smqnr* genes in clinical isolates of *Stenotrophomonas maltophilia* from a tertiary care hospital in southwest Iran. Iran J Basic Med Sci 22:872–877. https://doi.org/10.22038/ijbms.2019.31291.7540.
347. Chamieh A, El-Hajj G, Afif C, Azar E. 2020. Carbapenem resistant organisms: a 9-year surveillance and trends at Saint George University Medical Center. J Infect Public Health 13:2101–2106. https://doi.org/10.1016/j.jiph.2019.02.019.
348. Kanamori H, Yano H, Tanouchi A, Kakuta R, Endo S, Ichimura S, Ogawa M, Shimojima M, Inomata S, Ozawa D, Aoyagi T, Weber DJ, Kaku M. 2015. Prevalence of Sm*qnr* and plasmid-mediated quinolone resistance determinants in clinical isolates of *Stenotrophomonas maltophilia* from Japan: novel variants of Sm*qnr*. New Microbes New Infect 7:8–14. https://doi.org/10.1016/j.nmni.2015.04.009.
349. Margaritis A, Galani I, Chatzikonstantinou M, Petrikkos G, Souli M. 2017. Plasmid-mediated quinolone resistance determinants among Gram-negative bacteraemia isolates: a hidden threat. J Med Microbiol 66:266–275. https://doi.org/10.1099/jmm.0.000397.
350. Zhao J, Liu Y, Liu Y, Wang D, Ni W, Wang R, Liu Y, Zhang B. 2018. Frequency and genetic determinants of tigecycline resistance in clinically isolated *Stenotrophomonas maltophilia* in Beijing. China. Front Microbiol 9:549. https://doi.org/10.3389/fmicb.2018.00549.
351. Zgair AK, Chhibber S. 2011. Adhesion of *Stenotrophomonas maltophilia* to mouse tracheal mucus is mediated through flagella. J Med Microbiol 60:1032–1037. https://doi.org/10.1099/jmm.0.026377-0.
352. Zgair AK, Chhibber S. 2011. Immunoassay method to check the flagellin mediated binding of *Stenotrophomonas maltophilia* to polystyrene. Mikrobiologiia 80:136–138.
353. Zgair AK, Chhibber S. 2012. Immunological and biological relationship among flagellin of *Pseudomonas aeruginosa*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia*. Microbiology 81:342–347. https://doi.org/10.1134/S0026261712030174.
354. Zgair AK, Chhibber S. 2012. *Stenotrophomonas maltophilia* flagellin restricts bacterial colonization in BALB/c mouse lung *in vivo*. FEMS Immunol Med Microbiol 66:191–200. https://doi.org/10.1111/j.1574-695X.2012.00999.x.
355. Pompilio A, Crocetta V, Di Bonaventura G. 2018. *Stenotrophomonas maltophilia* mutant lacking flagella remains virulent in DBA/2N mice but is less efficient in stimulating TNF-α expression. FEMS Microbiol Lett 365:fny205. https://doi.org/10.1093/femsle/fny205.
356. Yang J-G, Shih M-S, Kuo W-T, Chin K-H, Shen G-H, Chou S-H. 2014. Crystallization of the N-terminal regulatory domain of the enhancer-binding protein FleQ from *Stenotrophomonas maltophilia*. Acta Crystallogr F Struct Biol Commun 70:326–330. https://doi.org/10.1107/S2053230X14001514.
357. Huang H-H, Chen W-C, Lin C-W, Lin Y-T, Ning H-C, Chang Y-C, Yang T-C. 2017. Relationship of the CreBC two-component regulatory system and inner membrane protein CreD with swimming motility in *Stenotrophomonas maltophilia*. PLoS One 12:e0174704. https://doi.org/10.1371/journal.pone.0174704.
358. Huang H-H, Lin Y-T, Chen W-C, Huang Y-W, Chen S-J, Yang T-C. 2015. Expression and functions of CreD, an inner membrane protein in *Stenotrophomonas maltophilia*. PLoS One 10:e0145009. https://doi.org/10.1371/journal.pone.0145009.
359. Kalidasan V, Neela VK. 2020. Twitching motility of *Stenotrophomonas maltophilia* under iron limitation: *in-silico*, phenotypic and proteomic approaches. Virulence 11:104–112. https://doi.org/10.1080/21505594.2020.1713649.
360. Winstanley C, O'Brien S, Brockhurst MA. 2016. *Pseudomonas aeruginosa* evolutionary adaptation and diversification in cystic fibrosis chronic lung infections. Trends Microbiol 24:327–337. https://doi.org/10.1016/j.tim.2016.01.008.
361. Zgair AK, Chhibber S. 2011. Adhering ability of *Stenotrophomonas maltophilia* is dependent on growth conditions. Microbiology 80:466. https://doi.org/10.1134/S0026261711040230.
362. Ramos-Hegazy L, Chakravarty S, Anderson GG. 2020. Phosphoglycerate mutase affects *Stenotrophomonas maltophilia* attachment to biotic and abiotic surfaces. Microbes Infect 22:60–64. https://doi.org/10.1016/j.micinf.2019.08.001.
363. Mizusawa M, Konuma T, Kato S, Isobe M, Shibata H, Suzuki M, Takahashi O, Oiwa-Monna M, Takahashi S, Tojo A. 2020. Clinical outcomes of persistent colonization with multidrug-resistant Gram-negative rods in adult patients undergoing single cord blood transplantation. Int J Hematol 111:858–868. https://doi.org/10.1007/s12185-020-02854-5.
364. Rouf R, Karaba SM, Dao J, Cianciotto NP. 2011. *Stenotrophomonas maltophilia* strains replicate and persist in the murine lung, but to significantly different degrees. Microbiology (Reading) 157:2133–2142. https://doi.org/10.1099/mic.0.048157-0.
365. Dantam J, Subbaraman LN, Jones L. 2020. Adhesion of *Pseudomonas aeruginosa*, *Achromobacter xylosoxidans*, *Delftia acidovorans*, *Stenotrophomonas maltophilia* to contact lenses under the influence of an artificial tear solution. Biofouling 36:32–43. https://doi.org/10.1080/08927014.2019.1710832.
366. Tran PL, Huynh E, Pham P, Lacky B, Jarvis C, Mosley T, Hamood AN, Hanes R, Reid T. 2017. Organoselenium polymer inhibits biofilm formation in polypropylene contact lens case material. Eye Contact Lens 43:110–115. https://doi.org/10.1097/ICL.0000000000000239.
367. Liu LY, Seo J, McCanna DJ, Subbaraman LN, Jones LW. 2016. Assessment of biofilm formation of *E. meningoseptica*, *D. acidovorans*, and *S. maltophilia* in lens cases and their growth on recovery media. Cont Lens Anterior Eye 39:117–123. https://doi.org/10.1016/j.clae.2015.09.001.
368. Kilvington S, Shovlin J, Nikolic M. 2013. Identification and susceptibility to multipurpose disinfectant solutions of bacteria isolated from contact lens storage cases of patients with corneal infiltrative events. Cont Lens Anterior Eye 36:294–298. https://doi.org/10.1016/j.clae.2013.02.001.
369. Yamasaki K, Saito F, Ota R, Kilvington S. 2018. Antimicrobial efficacy of a novel povidone iodine contact lens disinfection system. Cont Lens Anterior Eye 41:277–281. https://doi.org/10.1016/j.clae.2017.12.001.
370. Hinojosa JA, Patel NB, Zhu M, Robertson DM. 2017. Antimicrobial efficacy of contact lens care solutions against neutrophil-enhanced bacterial biofilms. Transl Vis Sci Technol 6:11. https://doi.org/10.1167/tvst.6.2.11.
371. Patel NB, Hinojosa JA, Zhu M, Robertson DM. 2018. Acceleration of the formation of biofilms on contact lens surfaces in the presence of neutrophil-derived cellular debris is conserved across multiple genera. Mol Vis 24:94–104.
372. Vijay AK, Willcox MDP. 2018. Adhesion of *Stenotrophomonas maltophilia*, *Delftia acidovorans*, and *Achromobacter xylosoxidans* to contact lenses. Eye Contact Lens 44:S120–S126. https://doi.org/10.1097/ICL.0000000000000425.
373. Williams TJ, Willcox MD, Schneider RP. 2012. Interactions of ocular isolates of Gram-negative bacteria with lactoferrin. Eye Contact Lens 38:208–213. https://doi.org/10.1097/ICL.0b013e318248292c.
374. Aguilera-Correa J-J, Mediero A, Conesa-Buendía F-M, Conde A, Arenas M-Á, de-Damborenea J-J, Esteban J. 2018. Microbiological and cellular evaluation of a fluorine-phosphorus-doped titanium alloy, a novel antibacterial and osteostimulatory biomaterial with potential applications in orthopedic surgery. Appl Environ Microbiol 85:e02271-18. https://doi.org/10.1128/AEM.02271-18.
375. Ben Chobba M, Messaoud M, Weththimuni ML, Bouaziz J, Licchelli M, De Leo F, Urzì C. 2019. Preparation and characterization of photocatalytic Gd-doped TiO_2 nanoparticles for water treatment. Environ Sci Pollut Res Int 26:32734–32745. https://doi.org/10.1007/s11356-019-04680-7.
376. Cianciotto NP, White RC. 2017. Expanding role of type II secretion in bacterial pathogenesis and beyond. Infect Immun 85:e00014-17. https://doi.org/10.1128/IAI.00014-17.
377. Karaba SM, White RC, Cianciotto NP. 2013. *Stenotrophomonas maltophilia* encodes a type II protein secretion system that promotes detrimental effects on lung epithelial cells. Infect Immun 81:3210–3219. https://doi.org/10.1128/IAI.00546-13.
378. DuMont AL, Cianciotto NP. 2017. *Stenotrophomonas maltophilia* serine protease StmPr1 induces matrilysis, anoikis, and protease-activated receptor-2 activation in human lung epithelial cells. Infect Immun 85:e00544-17. https://doi.org/10.1128/IAI.00544-17.
379. DuMont AL, Karaba SM, Cianciotto NP. 2015. Type II secretion-dependent degradative and cytotoxic activities mediated by the *Stenotrophomonas maltophilia* serine proteases StmPr1 and StmPr2. Infect Immun 83:3825–3837. https://doi.org/10.1128/IAI.00672-15.
380. Molloy K, Cagney G, Dillon ET, Wynne K, Greene CM, McElvaney NG. 2020. Impaired airway epithelial barrier integrity in response to *Stenotrophomonas maltophilia* proteases, novel insights using cystic fibrosis bronchial epithelial cell secretomics. Front Immunol 11:198. https://doi.org/10.3389/fimmu.2020.00198.
381. Nas MY, White RC, DuMont AL, Lopez AE, Cianciotto NP. 2019. *Stenotrophomonas maltophilia* encodes a VirB/D4 type IV secretion system that modulates apoptosis in human cells and promotes competition against heterologous bacteria including *Pseudomonas aeruginosa*. Infect Immun 87:e00457-19. https://doi.org/10.1128/IAI.00457-19.

382. Bayer-Santos E, Cenens W, Matsuyama BY, Oka GU, Di Sessa G, Mininel IDV, Alves TL, Farah CS. 2019. The opportunistic pathogen *Stenotrophomonas maltophilia* utilizes a type IV secretion system for interbacterial killing. PLoS Pathog 15:e1007651. https://doi.org/10.1371/journal.ppat.1007651.
383. García CA, Passerini De Rossi B, Alcaraz E, Vay C, Franco M. 2012. Siderophores of *Stenotrophomonas maltophilia*: detection and determination of their chemical nature. Rev Argent Microbiol 44:150–154.
384. Nas MY, Cianciotto NP. 2017. *Stenotrophomonas maltophilia* produces an EntC-dependent catecholate siderophore that is distinct from enterobactin. Microbiology (Reading) 163:1590–1603. https://doi.org/10.1099/mic.0.000545.
385. Kalidasan V, Azman A, Joseph N, Kumar S, Awang Hamat R, Neela VK. 2018. Putative iron acquisition systems in *Stenotrophomonas maltophilia*. Molecules 23:2048. https://doi.org/10.3390/molecules23082048.
386. Azman A, Vasodavan K, Joseph N, Kumar S, Hamat RA, Nordin SA, Aizat WM, van Belkum A, Neela VK. 2019. Physiological and proteomic analysis of *Stenotrophomonas maltophilia* grown under the iron-limited condition. Future Microbiol 14:1417–1428. https://doi.org/10.2217/fmb-2019-0174.
387. García CA, Alcaraz ES, Franco MA, Passerini d. R B. 2015. Iron is a signal for *Stenotrophomonas maltophilia* biofilm formation, oxidative stress response, OMPs expression, and virulence. Front Microbiol 6:926. https://doi.org/10.3389/fmicb.2015.00926.
388. Kalidasan V, Joseph N, Kumar S, Hamat RA, Neela VK. 2018. Iron and virulence in *Stenotrophomonas maltophilia*: all we know so far. Front Cell Infect Microbiol 8:401. https://doi.org/10.3389/fcimb.2018.00401.
389. Liao C-H, Chen W-C, Li L-H, Lin Y-T, Pan S-Y, Yang T-C. 2020. AmpR of Stenotrophomonas maltophilia is involved in stenobactin synthesis and enhanced β-lactam resistance in an iron-depleted condition. J Antimicrob Chemother 75:3544–3551. https://doi.org/10.1093/jac/dkaa358.
390. Huang Y-W, Huang H-H, Huang K-H, Chen W-C, Lin Y-T, Hsu C-C, Yang T-C. 2019. AmpI functions as an iron exporter to alleviate β-lactam-mediated reactive oxygen species stress in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 63:e02467-18. https://doi.org/10.1128/AAC.02467-18.
391. Devos S, Stremersch S, Raemdonck K, Braeckmans K, Devreese B. 2016. Intra- and interspecies effects of outer membrane vesicles from *Stenotrophomonas maltophilia* on β-lactam resistance. Antimicrob Agents Chemother 60:2516–2518. https://doi.org/10.1128/AAC.02171-15.
392. Devos S, Van Oudenhove L, Stremersch S, Van Putte W, De RR, Van Driessche G, Vitse J, Raemdonck K, Devreese B. 2015. The effect of imipenem and diffusible signaling factors on the secretion of outer membrane vesicles and associated Ax21 proteins in *Stenotrophomonas maltophilia*. Front Microbiol 6:298. https://doi.org/10.3389/fmicb.2015.00298.
393. Kim YJ, Jeon H, Na SH, Kwon HI, Selasi GN, Nicholas A, Park TI, Lee SH, Lee JC. 2016. *Stenotrophomonas maltophilia* outer membrane vesicles elicit a potent inflammatory response *in vitro* and *in vivo*. Pathog Dis 74:ftw104. https://doi.org/10.1093/femspd/ftw104.
394. Li Y, Tang X, Zhao Z, Wang H, Wang X, Shang X, Liu P, Kou Z, Jiang Y, Li Y. 2019. Intranasal immunization with recombinant outer membrane protein A induces protective immune response against *Stenotrophomonas maltophilia* infection. PLoS One 14:e0214596. https://doi.org/10.1371/journal.pone.0214596.
395. Xu G, Tang X, Shang X, Li Y, Wang J, Yue J, Li Y. 2018. Identification of immunogenic outer membrane proteins and evaluation of their protective efficacy against *Stenotrophomonas maltophilia*. BMC Infect Dis 18:347. https://doi.org/10.1186/s12879-018-3258-7.
396. Wu C-J, Huang Y-W, Lin Y-T, Yang T-C. 2016. Inactivation of lytic transglycosylases increases susceptibility to aminoglycosides and macrolides by altering the outer membrane permeability of *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 60:3236–3239. https://doi.org/10.1128/AAC.03026-15.
397. Ferrer-Navarro M, Torrent G, Mongiardini E, Conchillo-Solé O, Gibert I, Daura X. 2016. Proteomic analysis of outer membrane proteins and vesicles of a clinical isolate and a collection strain of *Stenotrophomonas maltophilia*. J Proteomics 142:122–129. https://doi.org/10.1016/j.jprot.2016.05.001.
398. Devos S, Van Putte W, Vitse J, Van Driessche G, Stremersch S, Van Den Broek W, Raemdonck K, Braeckmans K, Stahlberg H, Kudryashev M, Savvides SN, Devreese B. 2017. Membrane vesicle secretion and prophage induction in multidrug-resistant *Stenotrophomonas maltophilia* in response to ciprofloxacin stress. Environ Microbiol 19:3930–3937. https://doi.org/10.1111/1462-2920.13793.
399. Chen Y-Y, Wu H-C, Lin J-W, Weng S-F. 2015. Functional properties of the major outer membrane protein in *Stenotrophomonas maltophilia*. J Microbiol 53:535–543. https://doi.org/10.1007/s12275-015-5202-5.
400. Sun E, Liang G, Wang L, Wei W, Lei M, Song S, Han R, Wang Y, Qi W. 2016. Antimicrobial susceptibility of hospital acquired *Stenotrophomonas maltophilia* isolate biofilms. Braz J Infect Dis 20:365–373. https://doi.org/10.1016/j.bjid.2016.04.002.
401. Pompilio A, Savini V, Fiscarelli E, Gherardi G, Di Bonaventura G. 2020. Clonal diversity, biofilm formation, and antimicrobial resistance among *Stenotrophomonas maltophilia* strains from cystic fibrosis and non-cystic fibrosis patients. Antibiotics (Basel) 9:15. https://doi.org/10.3390/antibiotics9010015.
402. Madsen JS, Burmølle M, Hansen LH, Sørensen SJ. 2012. The interconnection between biofilm formation and horizontal gene transfer. FEMS Immunol Med Microbiol 65:183–195. https://doi.org/10.1111/j.1574-695X.2012.00960.x.
403. Nolan LM, Turnbull L, Katrib M, Osvath SR, Losa D, Lazenby JJ, Whitchurch CB. 2020. *Pseudomonas aeruginosa* is capable of natural transformation in biofilms. Microbiology (Reading) 166:995–1003. https://doi.org/10.1099/mic.0.000956.
404. Varposhti M, Entezari F, Feizabadi MM. 2014. Synergistic interactions in mixed-species biofilms of pathogenic bacteria from the respiratory tract. Rev Soc Bras Med Trop 47:649–652. https://doi.org/10.1590/0037-8682-0262-2013.
405. Melloul E, Luiggi S, Anaïs L, Arné P, Costa JM, Fihman V, Briard B, Dannaoui E, Guillot J, Decousser JW, Beauvais A, Botterel F. 2016. Characteristics of *Aspergillus fumigatus* in association with *Stenotrophomonas maltophilia* in an *in vitro* model of mixed biofilm. PLoS One 11:e0166325. https://doi.org/10.1371/journal.pone.0166325.
406. Martínez P, Huedo P, Martinez-Servat S, Planell R, Ferrer-Navarro M, Daura X, Yero D, Gibert I. 2015. *Stenotrophomonas maltophilia* responds to exogenous AHL signals through the LuxR solo SmoR (Smlt1839). Front Cell Infect Microbiol 5:41. https://doi.org/10.3389/fcimb.2015.00041.
407. Pompilio A, Crocetta V, De Nicola S, Verginelli F, Fiscarelli E, Di Bonaventura G. 2015. Cooperative pathogenicity in cystic fibrosis: *Stenotrophomonas maltophilia* modulates *Pseudomonas aeruginosa* virulence in mixed biofilm. Front Microbiol 6:951. https://doi.org/10.3389/fmicb.2015.00951.
408. Magalhães AP, Lopes SP, Pereira MO. 2016. Insights into cystic fibrosis polymicrobial consortia: the role of species interactions in biofilm development, phenotype, and response to in-use antibiotics. Front Microbiol 7:2146. https://doi.org/10.3389/fmicb.2016.02146.
409. Melloul E, Roisin L, Durieux M-F, Woerther P-L, Jenot D, Risco V, Guillot J, Dannaoui E, Decousser J-W, Botterel F. 2018. Interactions of *Aspergillus fumigatus* and *Stenotrophomonas maltophilia* in an *in vitro* mixed biofilm model: does the strain matter? Front Microbiol 9:2850. https://doi.org/10.3389/fmicb.2018.02850.
410. Bruchmann J, Sachsenheimer K, Rapp BE, Schwartz T. 2015. Multi-channel microfluidic biosensor platform applied for online monitoring and screening of biofilm formation and activity. PLoS One 10:e0117300. https://doi.org/10.1371/journal.pone.0117300.
411. Kang X-M, Wang F-F, Zhang H, Zhang Q, Qian W. 2015. Genome-wide identification of genes necessary for biofilm formation by nosocomial pathogen *Stenotrophomonas maltophilia* reveals that orphan response regulator FsnR is a critical modulator. Appl Environ Microbiol 81:1200–1209. https://doi.org/10.1128/AEM.03408-14.
412. Liu W, Tian X-Q, Wei J-W, Ding L-L, Qian W, Liu Z, Wang F-F. 2017. BsmR degrades c-di-GMP to modulate biofilm formation of nosocomial pathogen *Stenotrophomonas maltophilia*. Sci Rep 7:4665. https://doi.org/10.1038/s41598-017-04763-w.
413. Zheng L, Wang F-F, Ren B-Z, Liu W, Liu Z, Qian W. 2016. Systematic mutational analysis of histidine kinase genes in the nosocomial pathogen *Stenotrophomonas maltophilia* identifies BfmAK system control of biofilm development. Appl Environ Microbiol 82:2444–2456. https://doi.org/10.1128/AEM.03951-15.
414. Barber CE, Tang JL, Feng JX, Pan MQ, Wilson TJG, Slater H, Dow JM, Williams P, Daniels MJ. 1997. A novel regulatory system required for pathogenicity of *Xanthomonas campestris* is mediated by a small diffusible signal molecule. Mol Microbiol 24:555–566. https://doi.org/10.1046/j.1365-2958.1997.3721736.x.
415. Fouhy Y, Scanlon K, Schouest K, Spillane C, Crossman L, Avison MB, Ryan RP, Dow JM. 2007. Diffusible signal factor-dependent cell-cell signaling and virulence in the nosocomial pathogen *Stenotrophomonas maltophilia*. J Bacteriol 189:4964–4968. https://doi.org/10.1128/JB.00310-07.

416. Fouhy Y, Scanlon K, Schouest K, Spillane C, Crossman L, Avison MB, Ryan RP, Dow JM. 2018. Retraction for Fouhy et al., "Diffusible signal factor-dependent cell-cell signaling and virulence in the nosocomial pathogen *Stenotrophomonas maltophili*a". J Bacteriol 200:e00235-18. https://doi.org/10.1128/JB.00235-18.
417. Twomey KB, O'Connell OJ, McCarthy Y, Dow JM, O'Toole GA, Plant BJ, Ryan RP. 2012. Bacterial *cis*-2-unsaturated fatty acids found in the cystic fibrosis airway modulate virulence and persistence of *Pseudomonas aeruginosa*. ISME J 6:939–950. https://doi.org/10.1038/ismej.2011.167.
418. Wang LH, He Y, Gao Y, Wu JE, Dong YH, He C, Wang SX, Weng LX, Xu JL, Tay L, Fang RX, Zhang LH. 2004. A bacterial cell-cell communication signal with cross-kingdom structural analogues. Mol Microbiol 51:903–912. https://doi.org/10.1046/j.1365-2958.2003.03883.x.
419. Alavi P, Müller H, Cardinale M, Zachow C, Sánchez MB, Martínez JL, Berg G. 2013. The DSF quorum sensing system controls the positive influence of *Stenotrophomonas maltophilia* on plants. PLoS One 8:e67103. https://doi.org/10.1371/journal.pone.0067103.
420. de Rossi BP, García C, Alcaraz E, Franco M. 2014. *Stenotrophomonas maltophilia* interferes via the DSF-mediated quorum sensing system with *Candida albicans* filamentation and its planktonic and biofilm modes of growth. Rev Argent Microbiol 46:288–297. https://doi.org/10.1016/S0325-7541(14)70084-7.
421. Huedo P, Coves X, Daura X, Gibert I, Yero D. 2018. Quorum sensing signaling and quenching in the multidrug-resistant pathogen *Stenotrophomonas maltophilia*. Front Cell Infect Microbiol 8:122. https://doi.org/10.3389/fcimb.2018.00122.
422. Huedo P, Yero D, Martínez-Servat S, Estibariz I, Planell R, Martínez P, Ruyra À, Roher N, Roca I, Vila J, Daura X, Gibert I. 2014. Two different *rpf* clusters distributed among a population of *Stenotrophomonas maltophilia* clinical strains display differential diffusible signal factor production and virulence regulation. J Bacteriol 196:2431–2442. https://doi.org/10.1128/JB.01540-14.
423. Huedo P, Yero D, Martinez-Servat S, Ruyra À, Roher N, Daura X, Gibert I. 2015. Decoding the genetic and functional diversity of the DSF quorum-sensing system in *Stenotrophomonas maltophilia*. Front Microbiol 6:761. https://doi.org/10.3389/fmicb.2015.00761.
424. An S, Tang J. 2018. Diffusible signal factor signaling regulates multiple functions in the opportunistic pathogen *Stenotrophomonas maltophilia*. BMC Res Notes 11:569. https://doi.org/10.1186/s13104-018-3690-1.
425. Alcaraz E, García C, Friedman L, Passerini de Rossi B. 2019. The rpf/DSF signalling system of *Stenotrophomonas maltophilia* positively regulates biofilm formation, production of virulence-associated factors and β-lactamase induction. FEMS Microbiol Lett 366:fnz069. https://doi.org/10.1093/femsle/fnz069.
426. Scoffone VC, Trespidi G, Chiarelli LR, Barbieri G, Buroni S. 2019. Quorum sensing as antivirulence target in cystic fibrosis pathogens. Int J Mol Sci 20:E1838. https://doi.org/10.3390/ijms20081838.
427. Yero D, Huedo P, Conchillo-Solé O, Martínez-Servat S, Mamat U, Coves X, Llanas F, Roca I, Vila J, Schaible UE, Daura X, Gibert I. 2020. Genetic variants of the DSF quorum sensing system in *Stenotrophomonas maltophilia* influence virulence and resistance phenotypes among genotypically diverse clinical isolates. Front Microbiol 11:1160. https://doi.org/10.3389/fmicb.2020.01160.
428. Han S-W, Lee S-W, Ronald PC. 2011. Secretion, modification, and regulation of Ax21. Curr Opin Microbiol 14:62–67. https://doi.org/10.1016/j.mib.2010.12.006.
429. McCarthy Y, Dow JM, Ryan RP. 2011. The Ax21 protein is a cell-cell signal that regulates virulence in the nosocomial pathogen *Stenotrophomonas maltophilia*. J Bacteriol 193:6375–6378. https://doi.org/10.1128/JB.05949-11.
430. McCarthy Y, Dow JM, Ryan RP. 2017. Retraction for McCarthy et al., "The Ax21 protein is a cell-cell signal that regulates virulence in the nosocomial pathogen *Stenotrophomonas maltophilia*". J Bacteriol 199:e00156-17. https://doi.org/10.1128/JB.00156-17.
431. Qian G, Zhou Y, Zhao Y, Song Z, Wang S, Fan J, Hu B, Venturi V, Liu F. 2013. Proteomic analysis reveals novel extracellular virulence-associated proteins and functions regulated by the diffusible signal factor (DSF) in *Xanthomonas oryzae* pv. *oryzicola*. J Proteome Res 12:3327–3341. https://doi.org/10.1021/pr4001543.
432. An S-Q, Tang J-I. 2018. The Ax21 protein influences virulence and biofilm formation in *Stenotrophomonas maltophilia*. Arch Microbiol 200:183–187. https://doi.org/10.1007/s00203-017-1433-7.
433. Di Bonaventura G, Pompilio A, Crocetta V, De Nicola S, Barbaro F, Giuliani L, D'Emilia E, Fiscarelli E, Bellomo RG, Saggini R. 2014. Exposure to extremely low-frequency magnetic field affects biofilm formation by cystic fibrosis pathogens. Future Microbiol 9:1303–1317. https://doi.org/10.2217/fmb.14.96.
434. Halstead FD, Thwaite JE, Burt R, Laws TR, Raguse M, Moeller R, Webber MA, Oppenheim BA. 2016. Antibacterial activity of blue light against nosocomial wound pathogens growing planktonically and as mature biofilms. Appl Environ Microbiol 82:4006–4016. https://doi.org/10.1128/AEM.00756-16.
435. Kanagasundaram NS, Perry JD, Hoenich NA, Clark RA, Fraser RA, Walton KE. 2015. Fluids for continuous renal replacement therapy–an evaluation of microbial integrity. Int J Artif Organs 38:13–16. https://doi.org/10.5301/ijao.5000378.
436. Biočanin M, Madi H, Vasiljević Z, Kojić M, Jovčić B, Lozo J. 2017. Temperature, pH and trimethoprim-sulfamethoxazole are potent inhibitors of biofilm formation by *Stenotrophomonas maltophilia* clinical isolates. Pol J Microbiol 66:433–438. https://doi.org/10.5604/01.3001.0010.6996.
437. Ratjen A, Yau Y, Wettlaufer J, Matukas L, Zlosnik JEA, Speert DP, LiPuma JJ, Tullis E, Waters V. 2015. *In vitro* efficacy of high-dose tobramycin against *Burkholderia cepacia* complex and *Stenotrophomonas maltophilia* isolates from cystic fibrosis patients. Antimicrob Agents Chemother 59:711–713. https://doi.org/10.1128/AAC.04123-14.
438. Pompilio A, Crocetta V, Verginelli F, Di Bonaventura G. 2016. *In vitro* activity of levofloxacin against planktonic and biofilm *Stenotrophomonas maltophilia* lifestyles under conditions relevant to pulmonary infection in cystic fibrosis, and relationship with SmeDEF multidrug efflux pump expression. FEMS Microbiol Lett 363:fnw145. https://doi.org/10.1093/femsle/fnw145.
439. Wang A, Wang Q, Kudinha T, Xiao S, Zhuo C. 2016. Effects of fluoroquinolones and azithromycin on biofilm formation of *Stenotrophomonas maltophilia*. Sci Rep 6:29701. https://doi.org/10.1038/srep29701.
440. Wu K, Yau YCW, Matukas L, Waters V. 2013. Biofilm compared to conventional antimicrobial susceptibility of *Stenotrophomonas maltophilia* isolates from cystic fibrosis patients. Antimicrob Agents Chemother 57:1546–1548. https://doi.org/10.1128/AAC.02215-12.
441. Gales AC, Jones RN, Sader HS. 2011. Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006–09). J Antimicrob Chemother 66:2070–2074. https://doi.org/10.1093/jac/dkr239.
442. Malinowski AM, McClarty BM, Robinson C, Spear W, Sanchez M, Sparkes TC, Brooke JS. 2017. Polysorbate 80 and polymyxin B inhibit *Stenotrophomonas maltophilia* biofilm. Diagn Microbiol Infect Dis 87:154–156. https://doi.org/10.1016/j.diagmicrobio.2016.11.008.
443. Jamal MA, Rosenblatt JS, Hachem RY, Ying J, Pravinkumar E, Nates JL, Chaftari AM, Raad II. 2014. Prevention of biofilm colonization by Gram-negative bacteria on minocycline-rifampin-impregnated catheters sequentially coated with chlorhexidine. Antimicrob Agents Chemother 58:1179–1182. https://doi.org/10.1128/AAC.01959-13.
444. Ding X, Yin B, Qian L, Zeng Z, Yang Z, Li H, Lu Y, Zhou S. 2011. Screening for novel quorum-sensing inhibitors to interfere with the formation of *Pseudomonas aeruginosa* biofilm. J Med Microbiol 60:1827–1834. https://doi.org/10.1099/jmm.0.024166-0.
445. Karunanidhi A, Thomas R, van Belkum A, Neela V. 2013. *In vitro* antibacterial and antibiofilm activities of chlorogenic acid against clinical isolates of *Stenotrophomonas maltophilia* including the trimethoprim/sulfamethoxazole resistant strain. Biomed Res Int 2013:392058. https://doi.org/10.1155/2013/392058.
446. Karunanidhi A, Ghaznavi-Rad E, Hamat RA, Pichika MR, Lung LTT, Mohd Fauzi F, Chigurupati S, van Belkum A, Neela V. 2018. Antibacterial and antibiofilm activities of nonpolar extracts of *Allium stipitatum* Regel. against multidrug resistant bacteria. Biomed Res Int 2018:9845075. https://doi.org/10.1155/2018/9845075.
447. Kim H-R, Lee D, Eom Y-B. 2018. Anti-biofilm and anti-virulence efficacy of celastrol against *Stenotrophomonas maltophilia*. Int J Med Sci 15:617–627. https://doi.org/10.7150/ijms.23924.
448. Thallinger B, Argirova M, Lesseva M, Ludwig R, Sygmund C, Schlick A, Nyanhongo GS, Guebitz GM. 2014. Preventing microbial colonisation of catheters: antimicrobial and antibiofilm activities of cellobiose dehydrogenase. Int J Antimicrob Agents 44:402–408. https://doi.org/10.1016/j.ijantimicag.2014.06.016.
449. Anđelković MV, Janković SM, Kostić MJ, Živković Zarić RS, Opančina VD, Živić MŽ, Milosavljević MJ, Pejčić AV. 2019. Antimicrobial treatment of

Stenotrophomonas maltophilia invasive infections: systematic review. J Chemother 31:297–306. https://doi.org/10.1080/1120009X.2019.1620405.
450. Ko J-H, Kang C-I, Cornejo-Juárez P, Yeh K-M, Wang C-H, Cho SY, Gözel MG, Kim S-H, Hsueh P-R, Sekiya N, Matsumura Y, Lee D-G, Cho S-Y, Shiratori S, Kim Y-J, Chung DR, Peck KR. 2019. Fluoroquinolones versus trimethoprim-sulfamethoxazole for the treatment of *Stenotrophomonas maltophilia* infections: a systematic review and meta-analysis. Clin Microbiol Infect 25:546–554. https://doi.org/10.1016/j.cmi.2018.11.008.
451. Awad LS, Abdallah DI, Mugharbil AM, Jisr TH, Droubi NS, El-Rajab NA, Moghnieh RA. 2018. An antibiotic stewardship exercise in the ICU: building a treatment algorithm for the management of ventilator-associated pneumonia based on local epidemiology and the 2016 Infectious Diseases Society of America/American Thoracic Society guidelines. Infect Drug Resist 11:17–28. https://doi.org/10.2147/IDR.S145827.
452. Shah MD, Coe KE, El Boghdadly Z, Wardlow LC, Dela-Pena JC, Stevenson KB, Reed EE. 2019. Efficacy of combination therapy versus monotherapy in the treatment of *Stenotrophomonas maltophilia* pneumonia. J Antimicrob Chemother 74:2055–2059. https://doi.org/10.1093/jac/dkz116.
453. Aoki T, Yoshizawa H, Yamawaki K, Yokoo K, Sato J, Hisakawa S, Hasegawa Y, Kusano H, Sano M, Sugimoto H, Nishitani Y, Sato T, Tsuji M, Nakamura R, Nishikawa T, Yamano Y. 2018. Cefiderocol (S-649266), a new siderophore cephalosporin exhibiting potent activities against *Pseudomonas aeruginosa* and other Gram-negative pathogens including multi-drug resistant bacteria: structure activity relationship. Eur J Med Chem 155:847–868. https://doi.org/10.1016/j.ejmech.2018.06.014.
454. Bassetti M, Echols R, Matsunaga Y, Ariyasu M, Doi Y, Ferrer R, Lodise TP, Naas T, Niki Y, Paterson DL, Portsmouth S, Torre-Cisneros J, Toyoizumi K, Wunderink RG, Nagata TD. 2020. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis 21:226–240. https://doi.org/10.1016/s1473-3099(20)30796-9.
455. Calvopiña K, Umland K-D, Rydzik AM, Hinchliffe P, Brem J, Spencer J, Schofield CJ, Avison MB. 2016. Sideromimic modification of lactivicin dramatically increases potency against extensively drug-resistant *Stenotrophomonas maltophilia* clinical isolates. Antimicrob Agents Chemother 60:4170–4175. https://doi.org/10.1128/AAC.00371-16.
456. Chen IH, Kidd JM, Abdelraouf K, Nicolau DP. 2019. Comparative *in vivo* antibacterial activity of human-simulated exposures of cefiderocol and ceftazidime against *Stenotrophomonas maltophilia* in the murine thigh model. Antimicrob Agents Chemother 63:e01558-19. https://doi.org/10.1128/AAC.01558-19.
457. Clinical and Laboratory Standards Institute. 2019. Performance standards for antimicrobial susceptibility testing, 29th informational supplement. CLSI supplement M100–S29. Clinical and Laboratory Standards Institute, Wayne, PA.
458. Delgado-Valverde M, Conejo MDC, Serrano L, Fernández-Cuenca F, Pascual Á. 2020. Activity of cefiderocol against high-risk clones of multidrug-resistant *Enterobacterales*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*. J Antimicrob Chemother 75:1840–1849. https://doi.org/10.1093/jac/dkaa117.
459. Golden AR, Adam HJ, Baxter M, Walkty A, Lagacé-Wiens P, Karlowsky JA, Zhanel GG. 2020. *In vitro* activity of cefiderocol, a novel siderophore cephalosporin, against Gram-negative bacilli isolated from patients in Canadian intensive care units. Diagn Microbiol Infect Dis 97:115012. https://doi.org/10.1016/j.diagmicrobio.2020.115012.
460. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. 2017. *In vitro* activity of the siderophore cephalosporin, cefiderocol, against a recent collection of clinically relevant Gram-negative bacilli from North America and Europe, including carbapenem-nonsusceptible isolates (SIDERO-WT-2014 Study). Antimicrob Agents Chemother 61:e00093-17. https://doi.org/10.1128/AAC.00093-17.
461. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. 2017. *In vitro* activity of the siderophore cephalosporin, cefiderocol, against carbapenem-nonsusceptible and multidrug-resistant isolates of Gram-negative bacilli collected worldwide in 2014 to 2016. Antimicrob Agents Chemother 62:e01968-17. https://doi.org/10.1128/AAC.01968-17.
462. Hsueh S-C, Lee Y-J, Huang Y-T, Liao C-H, Tsuji M, Hsueh P-R. 2019. *In vitro* activities of cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam and other comparative drugs against imipenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, all associated with bloodstream infections in Taiwan. J Antimicrob Chemother 74:380–386. https://doi.org/10.1093/jac/dky425.
463. Ito A, Kohira N, Bouchillon SK, West J, Rittenhouse S, Sader HS, Rhomberg PR, Jones RN, Yoshizawa H, Nakamura R, Tsuji M, Yamano Y. 2016. *In vitro* antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting Gram-negative bacteria. J Antimicrob Chemother 71:670–677. https://doi.org/10.1093/jac/dkv402.
464. Ito A, Sato T, Ota M, Takemura M, Nishikawa T, Toba S, Kohira N, Miyagawa S, Ishibashi N, Matsumoto S, Nakamura R, Tsuji M, Yamano Y. 2017. *In vitro* antibacterial properties of cefiderocol, a novel siderophore cephalosporin, against Gram-negative bacteria. Antimicrob Agents Chemother 62:e01454-17. https://doi.org/10.1128/AAC.01454-17.
465. Jacobs MR, Abdelhamed AM, Good CE, Rhoads DD, Hujer KM, Hujer AM, Domitrovic TN, Rudin SD, Richter SS, van Duin D, Kreiswirth BN, Greco C, Fouts DE, Bonomo RA. 2018. ARGONAUT-I: activity of cefiderocol (S-649266), a siderophore cephalosporin, against Gram-negative bacteria, including carbapenem-resistant nonfermenters and *Enterobacteriaceae* with defined extended-spectrum β-lactamases and carbapenemases. Antimicrob Agents Chemother 63:e01801-18. https://doi.org/10.1128/AAC.01801-18.
466. Karlowsky JA, Hackel MA, Tsuji M, Yamano Y, Echols R, Sahm DF. 2019. *In vitro* activity of cefiderocol, a siderophore cephalosporin, against Gram-negative bacilli isolated by clinical laboratories in North America and Europe in 2015–2016: SIDERO-WT-2015. Int J Antimicrob Agents 53:456–466. https://doi.org/10.1016/j.ijantimicag.2018.11.007.
467. Katsube T, Echols R, Wajima T. 2019. Pharmacokinetic and pharmacodynamic profiles of cefiderocol, a novel siderophore cephalosporin. Clin Infect Dis 69:S552–S558. https://doi.org/10.1093/cid/ciz828.
468. Nakamura R, Ito-Horiyama T, Takemura M, Toba S, Matsumoto S, Ikehara T, Tsuji M, Sato T, Yamano Y. 2019. *In vivo* pharmacodynamics study of cefiderocol, a novel parenteral siderophore cephalosporin, in murine thigh and lung infection models. Antimicrob Agents Chemother 63: e02031-18. https://doi.org/10.1128/AAC.02031-18.
469. Page MGP, Dantier C, Desarbre E, Gaucher B, Gebhardt K, Schmitt-Hoffmann A. 2011. *In vitro* and *in vivo* properties of BAL30376, a β-lactam and dual β-lactamase inhibitor combination with enhanced activity against Gram-negative bacilli that express multiple β-lactamases. Antimicrob Agents Chemother 55:1510–1519. https://doi.org/10.1128/AAC.01370-10.
470. Rolston KVI, Gerges B, Shelburne S, Aitken SL, Raad I, Prince RA. 2020. Activity of cefiderocol and comparators against isolates from cancer patients. Antimicrob Agents Chemother 64:e01955-19. https://doi.org/10.1128/AAC.01955-19.
471. Yamano Y. 2019. *In vitro* activity of cefiderocol against a broad range of clinically important Gram-negative bacteria. Clin Infect Dis 69:S544–S551. https://doi.org/10.1093/cid/ciz827.
472. Biagi M, Tan X, Wu T, Jurkovic M, Vialichka A, Meyer K, Mendes RE, Wenzler E. 2019. Activity of potential alternative treatment agents for *Stenotrophomonas maltophilia* isolates nonsusceptible to levofloxacin and/or trimethoprim-sulfamethoxazole. J Clin Microbiol 58:e01603-19. https://doi.org/10.1128/JCM.01603-19.
473. Flamm RK, Shortridge D, Castanheira M, Sader HS, Pfaller MA. 2019. *In vitro* activity of minocycline against U.S. isolates of *Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* complex: results from the SENTRY Antimicrobial Surveillance Program (2014–2018). Antimicrob Agents Chemother 63:e01154-19. https://doi.org/10.1128/AAC.01154-19.
474. Morrissey I, Olesky M, Hawser S, Lob SH, Karlowsky JA, Corey GR, Bassetti M, Fyfe C. 2019. *In vitro* activity of eravacycline against Gram-negative bacilli isolated in clinical laboratories worldwide from 2013 to 2017. Antimicrob Agents Chemother 64:e01699-19. https://doi.org/10.1128/AAC.01699-19.
475. Pfaller MA, Flamm RK, Duncan LR, Mendes RE, Jones RN, Sader HS. 2017. Antimicrobial activity of tigecycline and cefoperazone/sulbactam tested against 18,386 Gram-negative organisms from Europe and the Asia-Pacific region (2013–2014). Diagn Microbiol Infect Dis 88:177–183. https://doi.org/10.1016/j.diagmicrobio.2017.02.020.
476. Rizek C, Ferraz JR, van der Heijden IM, Giudice M, Mostachio AK, Paez J, Carrilho C, Levin AS, Costa SF. 2015. *In vitro* activity of potential old and new drugs against multidrug-resistant Gram-negatives. J Infect Chemother 21:114–117. https://doi.org/10.1016/j.jiac.2014.10.009.
477. Sader HS, Castanheira M, Farrell DJ, Flamm RK, Mendes RE, Jones RN. 2016. Tigecycline antimicrobial activity tested against clinical bacteria from Latin American medical centres: results from SENTRY Antimicrobial Surveillance Program (2011–2014). Int J Antimicrob Agents 48:144–150. https://doi.org/10.1016/j.ijantimicag.2016.04.021.

478. Zhanel GG, Baxter MR, Adam HJ, Sutcliffe J, Karlowsky JA. 2018. *In vitro* activity of eravacycline against 2213 Gram-negative and 2424 Gram-positive bacterial pathogens isolated in Canadian hospital laboratories: CANWARD surveillance study 2014–2015. Diagn Microbiol Infect Dis 91:55–62. https://doi.org/10.1016/j.diagmicrobio.2017.12.013.
479. Karamanlıoğlu D, Dizbay M. 2019. *In vitro* combination of tigecycline with other antibiotics in *Stenotrophomonas maltophilia* isolates. Turk J Med Sci 49:683–686. https://doi.org/10.3906/sag-1808-55.
480. Mojica MF, Papp-Wallace KM, Taracila MA, Barnes MD, Rutter JD, Jacobs MR, LiPuma JJ, Walsh TJ, Vila AJ, Bonomo RA. 2017. Avibactam restores the susceptibility of clinical isolates of *Stenotrophomonas maltophilia* to aztreonam. Antimicrob Agents Chemother 61:e00777-17. https://doi.org/10.1128/AAC.00777-17.
481. Calvopiña K, Hinchliffe P, Brem J, Heesom KJ, Johnson S, Cain R, Lohans CT, Fishwick CWG, Schofield CJ, Spencer J, Avison MB. 2017. Structural/mechanistic insights into the efficacy of nonclassical β-lactamase inhibitors against extensively drug resistant *Stenotrophomonas maltophilia* clinical isolates. Mol Microbiol 106:492–504. https://doi.org/10.1111/mmi.13831.
482. Mathy V, Grohs P, Compain F. 2018. *In vitro* activity of β-lactams in combination with avibactam against multidrug-resistant *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans* isolates from patients with cystic fibrosis. J Med Microbiol 67:1217–1220. https://doi.org/10.1099/jmm.0.000801.
483. Castanheira M, Huband MD, Mendes RE, Flamm RK. 2017. Meropenem-vaborbactam tested against contemporary Gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant *Enterobacteriaceae*. Antimicrob Agents Chemother 61:e00567-17. https://doi.org/10.1128/AAC.00567-17.
484. Livermore DM, Mushtaq S, Meunier D, Hopkins KL, Hill R, Adkin R, Chaudhry A, Pike R, Staves P, Woodford N, BSAC Resistance Surveillance Standing Committee. 2017. Activity of ceftolozane/tazobactam against surveillance and 'problem' *Enterobacteriaceae*, *Pseudomonas aeruginosa* and non-fermenters from the British Isles. J Antimicrob Chemother 72:2278–2289. https://doi.org/10.1093/jac/dkx136.
485. Livermore DM, Mushtaq S, Warner M, Turner SJ, Woodford N. 2018. Potential of high-dose cefepime/tazobactam against multiresistant Gram-negative pathogens. J Antimicrob Chemother 73:126–133. https://doi.org/10.1093/jac/dkx360.
486. Gramegna A, Millar BC, Blasi F, Elborn JS, Downey DG, Moore JE. 2018. *In vitro* antimicrobial activity of ceftolozane/tazobactam against *Pseudomonas aeruginosa* and other non-fermenting Gram-negative bacteria in adults with cystic fibrosis. J Glob Antimicrob Resist 14:224–227. https://doi.org/10.1016/j.jgar.2018.03.002.
487. Forrester JB, Steed LL, Santevecchi BA, Flume P, Palmer-Long GE, Bosso JA. 2018. *In vitro* activity of ceftolozane/tazobactam vs nonfermenting, Gram-negative cystic fibrosis isolates. Open Forum Infect Dis 5:ofy158. https://doi.org/10.1093/ofid/ofy158.
488. Emeraud C, Escaut L, Boucly A, Fortineau N, Bonnin RA, Naas T, Dortet L. 2019. Aztreonam plus clavulanate, tazobactam, or avibactam for treatment of infections caused by metallo-β-lactamase-producing Gram-negative bacteria. Antimicrob Agents Chemother 63:e00010-19. https://doi.org/10.1128/AAC.00010-19.
489. Farfour E, Trochu E, Devin C, Cardot Martin E, Limousin L, Roux A, Picard C, Jolly E, Vasse M, Lesprit P. 2018. Trends in ceftazidime-avibactam activity against multidrug-resistant organisms recovered from respiratory samples of cystic fibrosis patients. Transpl Infect Dis 20:e12955. https://doi.org/10.1111/tid.12955.
490. Caverly LJ, Spilker T, Kalikin LM, Stillwell T, Young C, Huang DB, LiPuma JJ. 2019. *In vitro* activities of β-lactam-β-lactamase inhibitor antimicrobial agents against cystic fibrosis respiratory pathogens. Antimicrob Agents Chemother 64:e01595-19. https://doi.org/10.1128/AAC.01595-19.
491. Moriceau C, Eveillard M, Lemarié C, Chenouard R, Pailhoriès H, Kempf M. 2020. *Stenotrophomonas maltophilia* susceptibility to ceftazidime-avibactam combination versus ceftazidime alone. Med Mal Infect 50:305–307. https://doi.org/10.1016/j.medmal.2020.01.003.
492. Attoub S, Mechkarska M, Sonnevend A, Radosavljevic G, Jovanovic I, Lukic ML, Conlon JM. 2013. Esculentin-2CHa: a host-defense peptide with differential cytotoxicity against bacteria, erythrocytes and tumor cells. Peptides 39:95–102. https://doi.org/10.1016/j.peptides.2012.11.004.
493. Mechkarska M, Attoub S, Sulaiman S, Pantic J, Lukic ML, Conlon JM. 2014. Anti-cancer, immunoregulatory, and antimicrobial activities of the frog skin host-defense peptides pseudhymenochirin-1Pb and pseudhymenochirin-2Pa. Regul Pept 194–195:69–76. https://doi.org/10.1016/j.regpep.2014.11.001.
494. Huertas Méndez NJ, Vargas Casanova Y, Gómez Chimbi AK, Hernández E, Leal Castro AL, Melo Diaz JM, Rivera Monroy ZJ, García Castañeda JE. 2017. Synthetic peptides derived from bovine lactoferricin exhibit antimicrobial activity against *E. coli* ATCC 11775, *S. maltophilia* ATCC 13636 and *S. enteritidis* ATCC 13076. Molecules 22:452. https://doi.org/10.3390/molecules22030452.
495. Pompilio A, Scocchi M, Pomponio S, Guida F, Di Primio A, Fiscarelli E, Gennaro R, Di Bonaventura G. 2011. Antibacterial and anti-biofilm effects of cathelicidin peptides against pathogens isolated from cystic fibrosis patients. Peptides 32:1807–1814. https://doi.org/10.1016/j.peptides.2011.08.002.
496. Pompilio A, Crocetta V, Scocchi M, Pomponio S, Di Vincenzo V, Mardirossian M, Gherardi G, Fiscarelli E, Dicuonzo G, Gennaro R, Di Bonaventura G. 2012. Potential novel therapeutic strategies in cystic fibrosis: antimicrobial and anti-biofilm activity of natural and designed α-helical peptides against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*. BMC Microbiol 12:145. https://doi.org/10.1186/1471-2180-12-145.
497. Mardirossian M, Pompilio A, Crocetta V, De Nicola S, Guida F, Degasperi M, Gennaro R, Di Bonaventura G, Scocchi M. 2016. *In vitro* and *in vivo* evaluation of BMAP-derived peptides for the treatment of cystic fibrosis-related pulmonary infections. Amino Acids 48:2253–2260. https://doi.org/10.1007/s00726-016-2266-4.
498. Kumaraswamy M, Lin L, Olson J, Sun C-F, Nonejuie P, Corriden R, Döhrmann S, Ali SR, Amaro D, Rohde M, Pogliano J, Sakoulas G, Nizet V. 2016. Standard susceptibility testing overlooks potent azithromycin activity and cationic peptide synergy against MDR *Stenotrophomonas maltophilia*. J Antimicrob Chemother 71:1264–1269. https://doi.org/10.1093/jac/dkv487.
499. Payne JE, Dubois AV, Ingram RJ, Weldon S, Taggart CC, Elborn JS, Tunney MM. 2017. Activity of innate antimicrobial peptides and ivacaftor against clinical cystic fibrosis respiratory pathogens. Int J Antimicrob Agents 50:427–435. https://doi.org/10.1016/j.ijantimicag.2017.04.014.
500. Leitner I, Nemeth J, Feurstein T, Abrahim A, Matzneller P, Lagler H, Erker T, Langer O, Zeitlinger M. 2011. The third-generation P-glycoprotein inhibitor tariquidar may overcome bacterial multidrug resistance by increasing intracellular drug concentration. J Antimicrob Chemother 66:834–839. https://doi.org/10.1093/jac/dkq526.
501. Personne Y, Curtis MA, Wareham DW, Waite RD. 2014. Activity of the type I signal peptidase inhibitor MD3 against multidrug-resistant Gram-negative bacteria alone and in combination with colistin. J Antimicrob Chemother 69:3236–3243. https://doi.org/10.1093/jac/dku309.
502. Jones AK, Woods AL, Takeoka KT, Shen X, Wei J-R, Caughlan RE, Dean CR. 2017. Determinants of antibacterial spectrum and resistance potential of the elongation factor G inhibitor argyrin B in key Gram-negative pathogens. Antimicrob Agents Chemother 61:e02400-16. https://doi.org/10.1128/AAC.02400-16.
503. Buroni S, Makarov V, Scoffone VC, Trespidi G, Riccardi G, Chiarelli LR. 2020. The cell division protein FtsZ as a cellular target to hit cystic fibrosis pathogens. Eur J Med Chem 190:112132. https://doi.org/10.1016/j.ejmech.2020.112132.
504. Percival SL, Thomas J, Linton S, Okel T, Corum L, Slone W. 2012. The antimicrobial efficacy of silver on antibiotic-resistant bacteria isolated from burn wounds. Int Wound J 9:488–493. https://doi.org/10.1111/j.1742-481X.2011.00903.x.
505. Pérez-Díaz MA, Silva-Bermudez P, Jiménez-López B, Martínez-López V, Melgarejo-Ramírez Y, Brena-Molina A, Ibarra C, Baeza I, Martínez-Pardo ME, Reyes-Frías ML, Márquez-Gutiérrez E, Velasquillo C, Martínez-Castañon G, Martinez-Gutierrez F, Sánchez-Sánchez R. 2018. Silver-pig skin nanocomposites and mesenchymal stem cells: suitable antibiofilm cellular dressings for wound healing. J Nanobiotechnology 16:2. https://doi.org/10.1186/s12951-017-0331-0.
506. Pompilio A, Geminiani C, Bosco D, Rana R, Aceto A, Bucciarelli T, Scotti L, Di Bonaventura G. 2018. Electrochemically synthesized silver nanoparticles are active against planktonic and biofilm cells of *Pseudomonas aeruginosa* and other cystic fibrosis-associated bacterial pathogens. Front Microbiol 9:1349. https://doi.org/10.3389/fmicb.2018.01349.
507. Jasim R, Schneider EK, Han M, Azad MAK, Hussein M, Nowell C, Baker MA, Wang J, Li J, Velkov T. 2017. A fresh shine on cystic fibrosis inhalation therapy: antimicrobial synergy of polymyxin B in combination with silver nanoparticles. J Biomed Nanotechnol 13:447–457. https://doi.org/10.1166/jbn.2017.2355.

508. Morones-Ramirez JR, Winkler JA, Spina CS, Collins JJ. 2013. Silver enhances antibiotic activity against gram-negative bacteria. Sci Transl Med 5:190ra81. https://doi.org/10.1126/scitranslmed.3006276.
509. Ortega A, Farah S, Tranque P, Ocaña AV, Nam-Cha SH, Beyth N, Gómez-Roldán C, Pérez-Tanoira R, Domb AJ, Pérez-Martínez FC, Pérez-Martínez J. 2015. Antimicrobial evaluation of quaternary ammonium polyethyleneimine nanoparticles against clinical isolates of pathogenic bacteria. IET Nanobiotechnol 9:342–348. https://doi.org/10.1049/iet-nbt.2014.0078.
510. Pollini S, Di Pilato V, Landini G, Di Maggio T, Cannatelli A, Sottotetti S, Cariani L, Aliberti S, Blasi F, Sergio F, Rossolini GM, Pallecchi L. 2018. *In vitro* activity of *N*-acetylcysteine against *Stenotrophomonas maltophilia* and *Burkholderia cepacia* complex grown in planktonic phase and biofilm. PLoS One 13:e0203941. https://doi.org/10.1371/journal.pone.0203941.
511. Ciacci N, Boncompagni S, Valzano F, Cariani L, Aliberti S, Blasi F, Pollini S, Rossolini GM, Pallecchi L. 2019. *In vitro* synergism of colistin and *N*-acetylcysteine against *Stenotrophomonas maltophilia*. Antibiotics 8:101. https://doi.org/10.3390/antibiotics8030101.
512. Vidigal PG, Müsken M, Becker KA, Häussler S, Wingender J, Steinmann E, Kehrmann J, Gulbins E, Buer J, Rath PM, Steinmann J. 2014. Effects of green tea compound epigallocatechin-3-gallate against *Stenotrophomonas maltophilia* infection and biofilm. PLoS One 9:e92876. https://doi.org/10.1371/journal.pone.0092876.
513. Zhang Y, Wei J, Qiu Y, Niu C, Song Z, Yuan Y, Yue T. 2019. Structure-dependent inhibition of *Stenotrophomonas maltophilia* by polyphenol and its impact on cell membrane. Front Microbiol 10:2646. https://doi.org/10.3389/fmicb.2019.02646.
514. Chu W, Yang Y, Cai J, Kong H, Bai M, Fu X, Qin S, Zhang E. 2019. Synthesis and bioactivities of new membrane-active agents with aromatic linker: high selectivity and broad-spectrum antibacterial activity. ACS Infect Dis 5:1535–1545. https://doi.org/10.1021/acsinfecdis.9b00078.
515. Sader HS, Rhomberg PR, Duncan LR, Locher HH, Dale GE, Flamm RK. 2020. Antimicrobial activity of POL7306 tested against clinical isolates of Gram-negative bacteria collected worldwide. J Antimicrob Chemother 75:1518–1524. https://doi.org/10.1093/jac/dkaa020.
516. Esposito A, Vollaro A, Esposito EP, D'Alonzo D, Guaragna A, Zarrilli R, De Gregorio E. 2020. Antibacterial and antivirulence activity of glucocorticoid PYED-1 against *Stenotrophomonas maltophilia*. Antibiotics (Basel) 9:105. https://doi.org/10.3390/antibiotics9030105.
517. Luther A, Urfer M, Zahn M, Müller M, Wang SY, Mondal M, Vitale A, Hartmann JB, Sharpe T, Monte FL, Kocherla H, Cline E, Pessi G, Rath P, Modaresi SM, Chiquet P, Stiegeler S, Verbree C, Remus T, Schmitt M, Kolopp C, Westwood MA, Desjonquères N, Brabet E, Hell S, LePoupon K, Vermeulen A, Jaisson R, Rithié V, Upert G, Lederer A, Zbinden P, Wach A, Moehle K, Zerbe K, Locher HH, Bernardini F, Dale GE, Eberl L, Wollscheid B, Hiller S, Robinson JA, Obrecht D. 2019. Chimeric peptidomimetic antibiotics against Gram-negative bacteria. Nature 576:452–458. https://doi.org/10.1038/s41586-019-1665-6.
518. Singh VK, Kavita K, Prabhakaran R, Jha B. 2013. *cis*-9-Octadecenoic acid from the rhizospheric bacterium *Stenotrophomonas maltophilia* BJ01 shows quorum quenching and anti-biofilm activities. Biofouling 29:855–867. https://doi.org/10.1080/08927014.2013.807914.
519. Rahman L, Shinwari ZK, Iqrar I, Rahman L, Tanveer F. 2017. An assessment on the role of endophytic microbes in the therapeutic potential of *Fagonia indica*. Ann Clin Microbiol Antimicrob 16:53. https://doi.org/10.1186/s12941-017-0228-7.
520. Di Gregorio S, Lampis S, Vallini G. 2005. Selenite precipitation by a rhizospheric strain of *Stenotrophomonas* sp. isolated from the root system of *Astragalus bisulcatus*: a biotechnological perspective. Environ Int 31:233–-241. https://doi.org/10.1016/j.envint.2004.09.021.
521. Zonaro E, Lampis S, Turner RJ, Qazi SJ, Vallini G. 2015. Biogenic selenium and tellurium nanoparticles synthesized by environmental microbial isolates efficaciously inhibit bacterial planktonic cultures and biofilms. Front Microbiol 6:584. https://doi.org/10.3389/fmicb.2015.00584.
522. Cremonini E, Zonaro E, Donini M, Lampis S, Boaretti M, Dusi S, Melotti P, Lleo MM, Vallini G. 2016. Biogenic selenium nanoparticles: characterization, antimicrobial activity and effects on human dendritic cells and fibroblasts. Microb Biotechnol 9:758–771. https://doi.org/10.1111/1751-7915.12374.
523. Cremonini E, Boaretti M, Vandecandelaere I, Zonaro E, Coenye T, Lleo MM, Lampis S, Vallini G. 2018. Biogenic selenium nanoparticles synthesized by *Stenotrophomonas maltophilia* SeITE02 loose antibacterial and antibiofilm efficacy as a result of the progressive alteration of their organic coating layer. Microb Biotechnol 11:1037–1047. https://doi.org/10.1111/1751-7915.13260.
524. Liu J, Chen P, Zheng C, Huang YP. 2013. Characterization of maltocin P28, a novel phage tail-like bacteriocin from *Stenotrophomonas maltophilia*. Appl Environ Microbiol 79:5593–5600. https://doi.org/10.1128/AEM.01648-13.
525. Dong H, Zhu C, Chen J, Ye X, Huang Y-P. 2015. Antibacterial activity of *Stenotrophomonas maltophilia* endolysin P28 against both Gram-positive and Gram-negative bacteria. Front Microbiol 6:1299. https://doi.org/10.3389/fmicb.2015.01299.
526. Rojas-Solís D, Santoyo G. 2018. Data on the effect of *Pseudomonas stutzeri* E25 and *Stenotrophomonas maltophilia* CR71 culture supernatants on the mycelial growth of *Botrytis cinerea*. Data Brief 17:234–236. https://doi.org/10.1016/j.dib.2018.01.023.
527. Elhalag KM, Messiha NAS, Emara HM, Abdallah SA. 2016. Evaluation of antibacterial activity of *Stenotrophomonas maltophilia* against *Ralstonia solanacearum* under different application conditions. J Appl Microbiol 120:1629–1645. https://doi.org/10.1111/jam.13097.
528. Jankiewicz U, Larkowska E, Swiontek Brzezinska M. 2016. Production, characterization, gene cloning, and nematocidal activity of the extracellular protease from *Stenotrophomonas maltophilia* N4. J Biosci Bioeng 121:614–618. https://doi.org/10.1016/j.jbiosc.2015.11.011.
529. Wang Y-S, Zheng X-C, Hu Q-W, Zheng Y-G. 2015. Degradation of abamectin by newly isolated *Stenotrophomonas maltophilia* ZJB-14120 and characterization of its abamectin-tolerance mechanism. Res Microbiol 166:408–418. https://doi.org/10.1016/j.resmic.2015.04.002.
530. Alvarado-Gutiérrez ML, Ruiz-Ordaz N, Galíndez-Mayer J, Curiel-Quesada E, Santoyo-Tepole F. 2020. Degradation kinetics of carbendazim by *Klebsiella oxytoca*, *Flavobacterium johnsoniae*, and *Stenotrophomonas maltophilia* strains. Environ Sci Pollut Res Int 27:28518–28526. https://doi.org/10.1007/s11356-019-07069-8.
531. Alvarado-Gutiérrez ML, Ruiz-Ordaz N, Galíndez-Mayer J, Santoyo-Tepole F, Curiel-Quesada E, García-Mena J, Ahuatzi-Chacón D. 2017. Kinetics of carbendazim degradation in a horizontal tubular biofilm reactor. Bioprocess Biosyst Eng 40:519–528. https://doi.org/10.1007/s00449-016-1717-3.
532. Leng Y, Bao J, Song D, Li J, Ye M, Li X. 2017. Background nutrients affect the biotransformation of tetracycline by *Stenotrophomonas maltophilia* as revealed by genomics and proteomics. Environ Sci Technol 51:10476–10484. https://doi.org/10.1021/acs.est.7b02579.
533. Xiong W, Yin C, Peng W, Deng Z, Lin S, Liang R. 2020. Characteriation of an 17β-estradiol-degrading bacterium *Stenotrophomonas maltophilia* SJTL3 tolerant to adverse environmental factors. Appl Microbiol Biotechnol 104:1291–1305. https://doi.org/10.1007/s00253-019-10281-8.
534. Xiong W, Yin C, Wang Y, Lin S, Deng Z, Liang R. 2020. Characterization of an efficient estrogen-degrading bacterium *Stenotrophomonas maltophilia* SJTH1 in saline-, alkaline-, heavy metal-contained environments or solid soil and identification of four 17β-estradiol-oxidizing dehydrogenases. J Hazard Mater 385:121616. https://doi.org/10.1016/j.jhazmat.2019.121616.
535. Berg G, Martínez JL. 2015. Friends or foes: can we make a distinction between beneficial and harmful strains of the *Stenotrophomonas maltophilia* complex? Front Microbiol 6:241. https://doi.org/10.3389/fmicb.2015.00241.
536. Brooke JS, Di Bonaventura G, Berg G, Martinez JL. 2017. Editorial: a multidisciplinary look at *Stenotrophomonas maltophilia*: an emerging multi-drug-resistant global opportunistic pathogen. Front Microbiol 8:1511. https://doi.org/10.3389/fmicb.2017.01511.
537. Singh RP, Jha PN. 2017. The PGPR *Stenotrophomonas maltophilia* SBP-9 augments resistance against biotic and abiotic stress in wheat plants. Front Microbiol 8:1945. https://doi.org/10.3389/fmicb.2017.01945.
538. Alexander A, Singh VK, Mishra A. 2020. Halotolerant PGPR *Stenotrophomonas maltophilia* BJ01 induces salt tolerance by modulating physiology and biochemical activities of *Arachis hypogaea*. Front Microbiol 11:568289. https://doi.org/10.3389/fmicb.2020.568289.
539. Alexander A, Singh VK, Mishra A, Jha B. 2019. Plant growth promoting rhizobacterium *Stenotrophomonas maltophilia* BJ01 augments endurance against N_2 starvation by modulating physiology and biochemical activities of *Arachis hypogea*. PLoS One 14:e0222405. https://doi.org/10.1371/journal.pone.0222405.
540. Holmes AP, Hartis CE, Rollins LJ. 2020. High direct bilirubin associated with levofloxacin use in a neonate. J Pediatr Pharmacol Ther 25:64–67. https://doi.org/10.5863/1551-6776-25.1.64.

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