



Stenotrophomonas maltophilia as an Emerging Ubiquitous Pathogen: Looking Beyond Contemporary Antibiotic Therapy

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Specialty section:

This article was submitted to
Antimicrobials, Resistance and
Chemotherapy,
a section of the journal
Frontiers in Microbiology

Received: 02 August 2017

Accepted: 06 November 2017

Published: 30 November 2017

Citation:

Adegoke AA, Stenström TA and
Okoh AI (2017) *Stenotrophomonas*
maltophilia as an Emerging Ubiquitous
Pathogen: Looking Beyond
Contemporary Antibiotic Therapy.
Front. Microbiol. 8:2276.
doi: 10.3389/fmicb.2017.02276

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Stenotrophomonas maltophilia is a commensal and an emerging pathogen earlier noted in broad-spectrum life threatening infections among the vulnerable, but more recently as a pathogen in immunocompetent individuals. The bacteria are consistently being implicated in necrotizing otitis, cutaneous infections including soft tissue infection and keratitis, endocarditis, meningitis, acute respiratory tract infection (RTI), bacteraemia (with/without hematological malignancies), tropical pyomyositis, cystic fibrosis, septic arthritis, among others. *S. maltophilia* is also an environmental bacteria occurring in water, rhizospheres, as part of the animals' microflora, in foods, and several other microbiota. This review highlights clinical reports on *S. maltophilia* both as an opportunistic and as true pathogen. Also, biofilm formation as well as quorum sensing, extracellular enzymes, flagella, pili/fimbriae, small colony variant, other virulence or virulence-associated factors, the antibiotic resistance factors, and their implications are considered. Low outer membrane permeability, natural MDR efflux systems, and/or resistance genes, resistance mechanisms like the production of two inducible chromosomally encoded β -lactamases, and lack of carefully compiled patient history are factors that pose great challenges to the *S. maltophilia* control arsenals. The fluoroquinolone, some tetracycline derivatives and trimethoprim-sulphamethaxole (TMP-SMX) were reported as effective antibiotics with good therapeutic outcome. However, TMP-SMX resistance and allergies to sulfa together with high toxicity of fluoroquinolone are notable setbacks. *S. maltophilia*'s production and sustenance of biofilm by quorum sensing enhance their virulence, resistance to antibiotics and gene transfer, making quorum quenching an imperative step in *Stenotrophomonas* control. Incorporating several other proven approaches like bioengineered bacteriophage therapy, Epigallocatechin-3-gallate (EGCG), essential oil, nanoemulsions, and use of cationic compounds are promising alternatives which can be incorporated in *Stenotrophomonas* control arsenal.

Keywords: *Stenotrophomonas maltophilia*, sulfa, resistance genes, phage therapy, quorum quenching

INTRODUCTION

Stenotrophomonas maltophilia, previously called *Pseudomonas maltophilia* or *Xanthomonas maltophilia*, has emerged as an important nosocomial pathogen in clinical environments (Senol, 2004). It is responsible for various infectious diseases and death in hospitalized patients especially among the immunosuppressed, immunocompromised as well as those with medical implants (Robert et al., 1987; Calza et al., 2003; Cernohorská and Votava, 2004; Yeshurun et al., 2010; Hentrich et al., 2014). They are aerobic, glucose non-fermentative (but oxidize glucose and maltose), Gram-negative bacillus with slightly smaller size than other species in the *Stenotrophomonas* genus. They are motile with the aid of polar flagella and produce pigmented colonies (yellow) on MacConkey agar. *S. maltophilia* are catalase-positive, usually oxidase-negative (distinguishing feature with the genus) and lysine decarboxylase (Gilligan et al., 2003). **Table 1** shows the /biochemical characteristics of *S. maltophilia*. They are frequently isolated from water and soil (Adjidé et al., 2010); and from animals and plant materials (Borner et al., 2003; Berg et al., 2005; Furushita et al., 2005; Smeets et al., 2007). The bacteria frequently colonize patients' irrigation fluid (e.g., irrigation solutions, intravenous fluids etc.) and patient body fluid (respiratory aerosols or mucous, urine, and wound exudates) (Minkwitz and Berg, 2001). This review article attempts an overview of the implication of the commensal *S. maltophilia* in infections; their antibiotic regimen; therapeutic outcomes, reported genetic basis of observed resistances, and future approaches for therapy.

THE *S. MALTOPHILIA*: AN ENVIRONMENTAL COMMENSAL OR AN INFECTIOUS AGENT

S. maltophilia is a commensal organism of supposedly low virulence, yet vibrant as an opportunistic pathogen (Gnanasekaran and Bajaj, 2009). The bacteria's frequent colonization of fluids used in the hospital settings, irrigation solution, and/or invasive medical devices might become a vehicle to bypass normal host defenses to cause human infection (de Oliveira-Garcia et al., 2003). Hence, it has similar pathophysiology or pathogenesis with other non-fermentative aerobic organisms, in the face of immune systems as impedance factors. This in a way makes consultation cumbersome (Chang and Huang, 2000). *S. maltophilia* can cause a wide spectrum of serious infections (Calza et al., 2003; Cernohorská and Votava, 2004). Its ubiquity is ascertained in the environment as a commensal and in the hospital environment as an opportunistic pathogen in immunocompromised individuals or true pathogen in immunocompetent (Table 2). **Figure 1** illustrates various niches in environmental and clinical settings as well other factors associated with the bacteria. In the environment, the organism is found as the dominant species that usually outcompete the rhizospheric bacterial populations (Alavi et al., 2014). *S. maltophilia* can also be detected as environmental commensals and as aetiological agents respectively (Youenou et al., 2015). Youenou et al. (2015) reported that two clinical

TABLE 1 | Biochemical/growth characteristics of *S. maltophilia*.

Characteristics	Reaction/ results	Characteristics	Reaction/ results
Growth without NaCl	+	Carbon Adonitol utilization source	+
Growth with NaCl (1.5 and 3.0%)	+	Arabinose	+
Growth at 4°C	–	Adipate	+
Growth at 42°C	+/–	Amygdalin	+
Catalase	+	Mannose	+
Oxidase	+/–	Mannitol	+
Methionine as growth requirement	+	Caprate	–
Optimum growth temp of 35°C	+	Citrate	+
Hydrolysis of esculin	+	N-acetyl-glucosamine	+
Hydrolysis of gelatin	+	Fructose	+/–
Fermentation of glucose	–	Galactose	+/–
Motility	+	Gluconate	+
Nitrate reduction	+		
Lysine decarboxylase	+	Inositol	+
Arginine dihydrolase	–	Melbiose	–
Ornithine decarboxylase	–	Maltose	+
Tryptophane desaminase	–	Lactose	+
β-galactosidase	+/–	Trehalose	+/–
Methyl red	–	Tween 80 hydrolysis	+
Voges-Proskauer reaction	–	DNase production	+
H ₂ S production	–	Starch hydrolysis	–
		Urea hydrolysis	–
Phenylamine deaminase	–	"Acid production from maltose"	+
		"Acid production from glucose"	–

– means negative reaction or no growth; + means positive reaction or growth; +/- means variable reactions.

strains, one from Spain and the other from Australia clustered with an environmental strain from Brazil. The clinical strains, which were, identified as D457 and AU12-09 respectively as well as strain JV3 from the rhizosphere showed that both the environmental strain and the clinical strains are closely linked. This ubiquity of the potential pathogen may have effect on the epidemiology. The activities of the *S. maltophilia* in the root rhizosphere are beneficial (Ryan et al., 2009; Mendes et al., 2013; Alavi et al., 2014). This is because, the bacteria exert positive effects in plant growth and health, bioremediation and phytoremediation and synthesis of valuable macromolecules (Ting and Choong, 2009; Borland et al., 2016).

S. maltophilia, which is usually free living in the environment has been implicated in nosocomial infections and community based infections (Köseoglu et al., 2004; Meyer et al., 2006; Falagas et al., 2009). It has been reported as etiological agents in bacteraemia, ocular infection, endocarditis and RTIs (associated

TABLE 2 | *Stenotrophomonas maltophilia* as commensal in environment and etiological agent.

Habitat	Environmental (commensal)		Clinical/Subclinical (pathogen or opportunistic pathogen)		
	Rhizospheric Sources	References	Clinical Manifestation	References	
Terrestrial	Butternut roots'	Adegoke and Okoh, 2015	Necrotizing otitis	Borner et al., 2003; Al-Ghamdi et al., 2012	
	Potato roots	Dawam et al., 2013	Cutaneous infections	Smeets et al., 2007	
	Grass roots	Adegoke and Okoh, 2015	Endocarditis	Kim et al., 2002; Reynaud et al., 2015	
	Maize roots	Pereira et al., 2011	Meningitis	Platsouka et al., 2002; Libanore et al., 2004; Yemisen et al., 2008; Wang C. H. et al., 2014	
	Rice roots	Zhu et al., 2015	Soft tissue infection	Sakhnini et al., 2002	
	Medicago roots	Shen et al., 2015	Keratitits	Arora et al., 2005	
	Wheat roots	Majeed et al., 2015	Acute respiratory tract infection	Pathmanathan and Waterer, 2005	
	Sunflower roots	Ambrosini et al., 2012	Bacteraemia (usually with/without Hematological malignancies)	Labarca et al., 2000; Friedman et al., 2002; Senol et al., 2002; Al-Anazi et al., 2006; Jaidane et al., 2014	
	Water and wastewater	Municipal	Chang et al., 2005; Adjidé et al., 2010	Tropical pyomyositis	Thomas et al., 2010
				Cystic fibrosis	Talmaciu et al., 2000; Di Bonaventura et al., 2007; Hansen, 2012
Microfiltered water dispensers		Sacchetti et al., 2009			
River water		Nakatsu et al., 1995	Intestinal colonization resulting in diarrhea	Apisarnthanarak et al., 2003	
Saline subterranean Lake		Rivas et al., 2009	Septic arthritis	Aydemir et al., 2008	
Showerheads		Feazel et al., 2009			
Drinking water		Simões et al., 2007; Silbaq, 2009	Endocarditis	Takigawa et al., 2008	

with cystic fibrosis), wound infection and urinary tract infections (UTI) (Kim et al., 2002; Platsouka et al., 2002; Arora et al., 2005). It is also an aetiologic agents of meningitis, sepsis, skin, and soft tissue infections (SSTI) and it has been diagnosed with rare cases of pyomyositis (Gales et al., 2001; Platsouka et al., 2002; Sakhnini et al., 2002; Arora et al., 2005; Pathmanathan and Waterer, 2005; Al-Anazi et al., 2006; Yemisen et al., 2008; Thomas et al., 2010). Clinical skin presentations include primary cellulitis, cellulitis-like cutaneous metastasis or cellulitis or metastatic nodular skin lesions, gangrenous cellulitis, ecthyma gangrenosum, soft-tissue necrosis, and infected mucocutaneous ulcers (Denton and Kerr, 1998; Foo et al., 2002; Teo et al., 2006; Smeets et al., 2007). **Figure 2A** showed the ulcerated fingers infected with *S. maltophilia* (Trignano et al., 2014) in an immunocompetent person. This showed the true pathogenic status of the organism and it reveals the scourge of the organism which affect both intact skin (Sakhnini et al., 2002; Teo et al., 2006; Smeets et al., 2007) and ulcerated skin (Rit et al., 2015) in immunocompetent patients with non-healing outcome. This is exemplified by a case depicted in **Figure 2A** resulted in amputation of the fingers that would not heal due to *S. maltophilia*. Intact skin infections include metastatic cellulitis (Teo et al., 2006; Smeets et al., 2007), myositis (Downhour et al., 2002), and ecthyma gangrenosum among others. Some of these infections are depicted in **Table 2**. The organism has been frequently linked with cystic fibrosis (**Figure 1**) as an emerging potential pathogen, and pneumonia occurs more often as an expression of colonization with the bacteria (Pathmanathan and Waterer, 2005).

EPIDEMIOLOGY OF *S. MALTOPHILIA* INFECTION

As *S. maltophilia* is ubiquitous worldwide in the environment as commensal, its scourge in serious infections is equally global. In Germany, Meyer et al. (2006) determined changes in occurrence of *S. maltophilia* isolates per 1,000 patient days between 2001 and 2004 as nosocomial infection in intensive care unit (ICU), which revealed as high as 165 isolates per 1,000 in some study locations. Earlier, Apisarnthanarak et al. (2003) in a 6 weeks' surveillance study in Washington, USA reported a prevalence of 9.4% from stool samples. Labarca et al. (2000) in Los Angeles, USA observed an epidemic of *S. maltophilia* blood colonization among controlled allogenic bone marrow transplant patients. Also in Turkey Caylan et al. (2004), in a study from June 2000 to December 2001, isolated 44 strains as etiological agents from 41 hospitalized patients. Based on an epidemiological typing, Caylan et al. (2004) could conclude that the three outbreaks in the study area were caused by 12 strains showing the potentials of the bacteria in eliciting public health disturbances. Apisarnthanarak et al. (2003) noted that patients infected with *S. maltophilia* usually administer some antibiotics by self-medication, which usually fail due to multidrug resistance profile of the bacteria.

S. maltophilia has been reported as an etiological agent of several infectious diseases (Waters et al., 2012; Flores-Treviño et al., 2014; Pompilio et al., 2016). Quite a lot of clinical manifestation can be traced to the bacterial ability to change trait, together with virulence-associated factors which made them successful pathogens. Although, these dynamics are yet-to-being

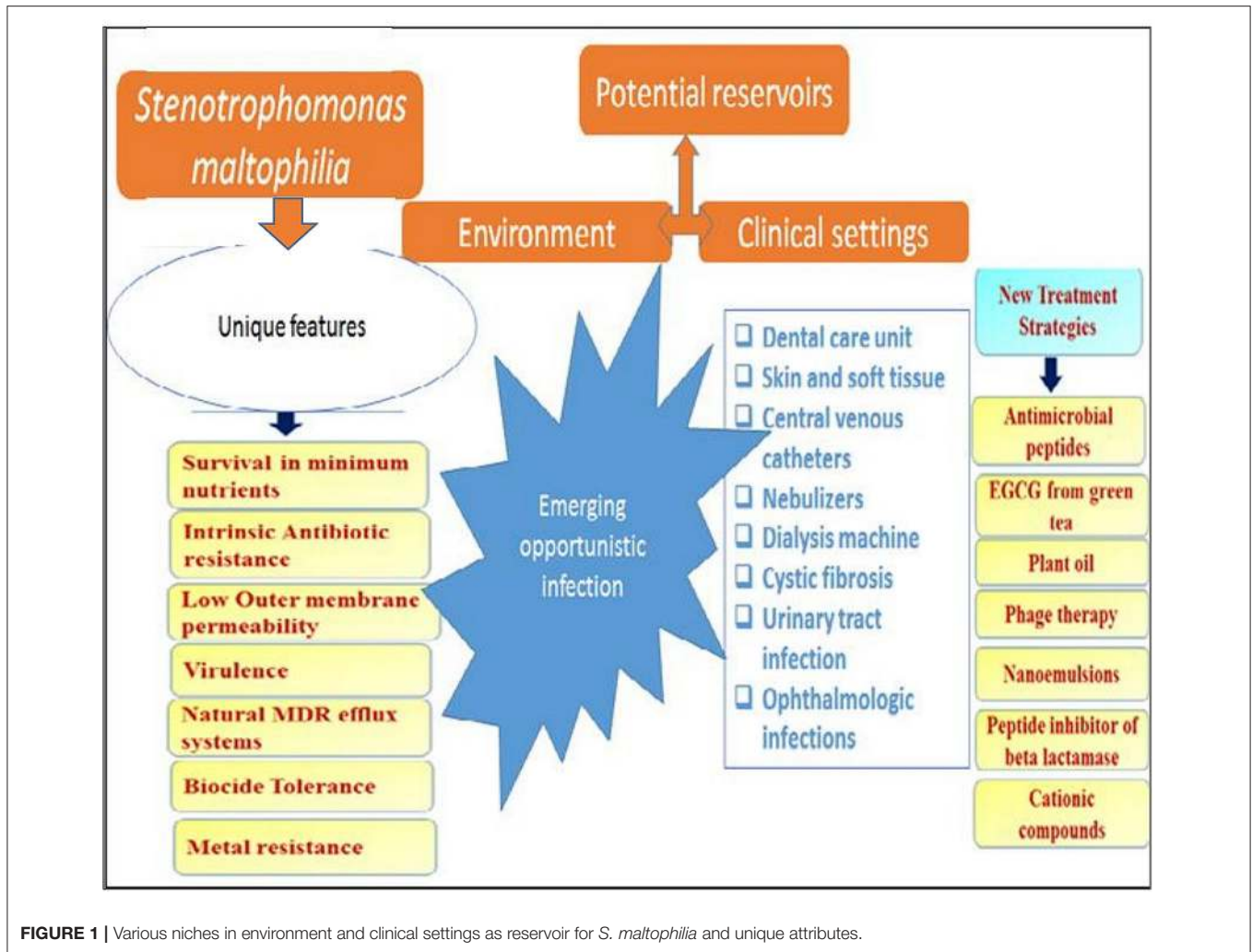
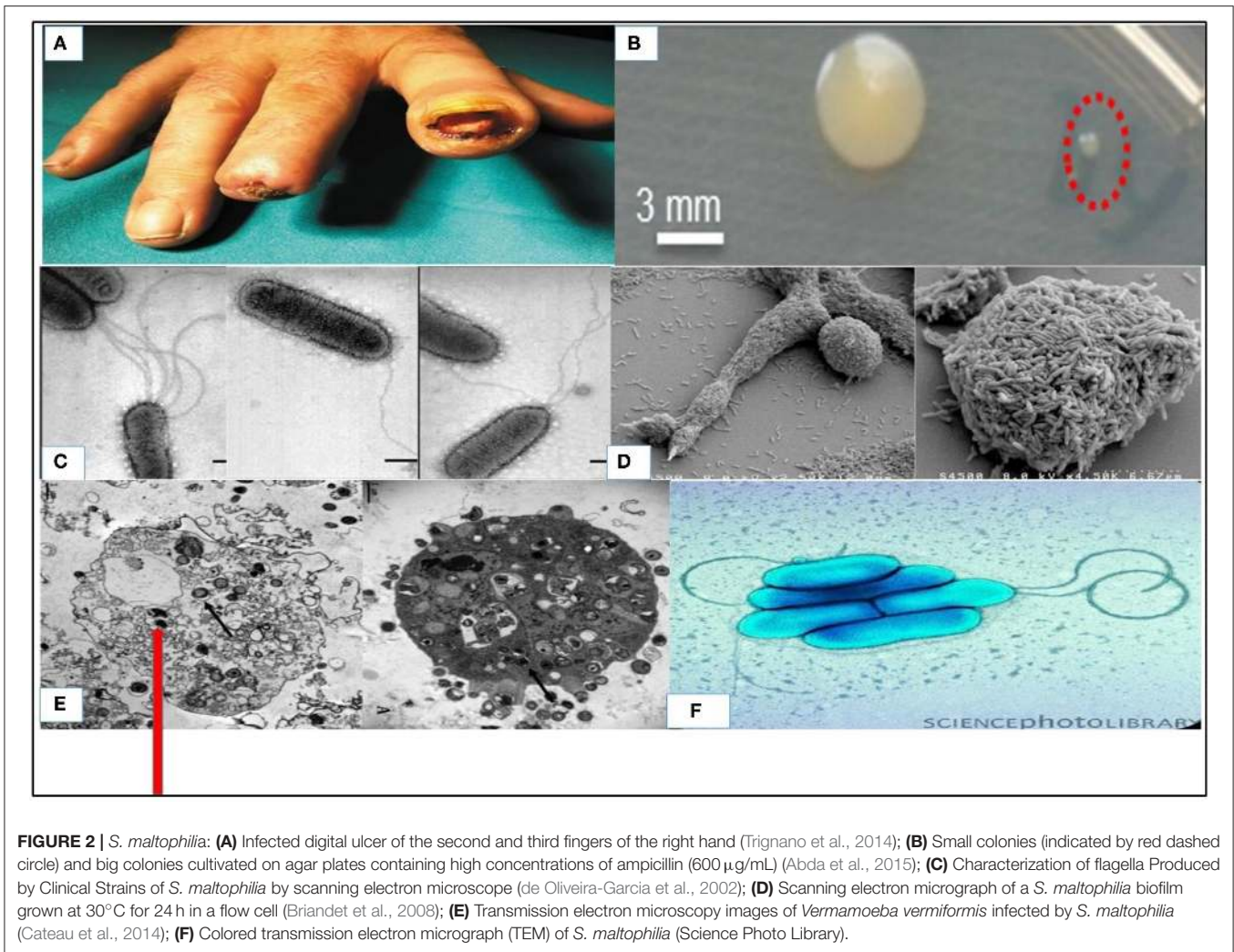


FIGURE 1 | Various niches in environment and clinical settings as reservoir for *S. maltophilia* and unique attributes.

fully understood (Pompilio et al., 2016), the effects on human health are undeniable. Both environmental and clinical strains have the virulence factors to colonize and advance to specific morbidity (Denton and Kerr, 1998; Pompilio et al., 2011). A report by Gulcan et al. (2004) confirmed 3 cases of *S. maltophilia* infection by molecular typing to be epidemiologically linked together. *S. maltophilia* cause pneumonia, UTI and surgical site infection (SSI), ophthalmologic infection, septic shock, and colonization of medical implants among immunosuppressed individuals (Al-Anazi and Al-Jasser, 2014). The bacteria have also been reported as an etiological agent of pyomyositis and otitis externa in immunocompetent adults (Thomas et al., 2010; Al-Ghamdi et al., 2012). Therefore, the organism behaves as both opportunistic and true pathogen. In 2012, a study from 59 hospital in United States of America and 15 in Europe implicated 187 isolates of *S. maltophilia* as etiological agents of RTIs out of 2968 cases, showing high frequency of occurrence of these bacteria as a pathogen and etiological agent.

Denis et al. (1977) reported two cases of, *S. maltophilia* meningitis in Africa 1977 (when the organism was still known as *Pseudomonas maltophilia*). Otherwise, evident cases from

Africa is generally sparse. Meanwhile, *S. africana* of the same genus as *S. maltophilia* is documented as a related opportunistic human pathogen across Africa (Drancourt et al., 1997). In recent times, the consistency of infection by the organism as reported worldwide (Huang et al., 2013; Wang C. H. et al., 2014; García-León et al., 2015; Reynaud et al., 2015) is quite alarming. *S. maltophilia* accounts for about 3.7% ($n = 10,000$) in hospital discharges and in the word of Abbott et al. (2011), “*S. maltophilia* is the third most common non-fermenting Gram-negative bacilli responsible for healthcare-associated infections, behind *P. aeruginosa* and *Acinetobacter* spp”. Rit et al. (2015) in India reported a case of non-healing wound resulting from colonization of *S. maltophilia* in an immunocompetent individual. In addition, an outbreak of drug resistant meningitis was reported by Wang C. H. et al. (2014) in Taiwan, China. These do not exclude multidrug resistant pacemaker infective endocarditis by this same organism as reported by Reynaud et al. (2015) in France and otitis external was reported by Al-Ghamdi et al. (2012) in Saudi Arabia. Some of these cases have been fatal (Thomas et al., 2010; Yeshurun et al., 2010; Huang et al., 2013; Hentrich et al., 2014). A recovery rate of 3.1%



in *S. maltophilia* infections was reported (Jones, 2010) in an 11-year study, done till 2008, among pneumonia patients on admission. The patients from the United States had highest recovery rates (3.3%), followed by EU (3.2%), then distantly by Southern America (2.3%) (Jones, 2010). Some of the clinical infections associated with these bacteria are depicted in **Table 2** below.

INFECTION PATHOGENESIS AND PATHOGENICITY

The unique features of *S. maltophilia* as reflected in **Figure 1**. Pathogenesis is by colonization, rather than infection, (Weber et al., 1999; Pathmanathan and Waterer, 2005), which is often accompanied by tissue invasion. Thus, it is often reported as colonization or infection (Juhász et al., 2014). Contaminated irrigation solutions and/or invasive medical devices may serve as “vehicle” with which it bypasses the non-specific immunity and causes human infections. Conditions like prolonged hospitalization, most common in ICU, implanted devices and mechanical ventilation, intravenous drug abuse, exposure to

wide-range of antibiotics, as well as malignancy can predispose patients to infection (Rolston et al., 2005) which may progress immediately. Kim et al. (2002) reported the establishment of *S. maltophilia* infection leading to endocarditis in a patient that had a replacement of valve with 27 mm Carbo Medics metallic due to severe rheumatic valvular disease. The duration of hospitalization of some patients before the onset of the *Stenotrophomonas* related clinical features and/or diagnosis is an important factor in nosocomial infection. Exemplifying case studies considered the duration of hospitalization before the onset of *S. maltophilia* bacteremia, which ranged from 11.5 to 24 days (Friedman et al., 2002; Senol et al., 2002; Lai et al., 2004) and about 3 weeks in other centers (Tsai et al., 2006). The burn patients usually develop *S. maltophilia* bacteremia after a week of staying in hospital (Krzewinski et al., 2001; Valdezate et al., 2001).

Table 3 gives an overview of the bacterial virulence factors and/or virulence associated factors in *S. maltophilia* and its potential application in diagnosis/therapy. As mentioned earlier, the detail of pathogenesis of *S. maltophilia* is not fully understood, but a number of studies have thrown light on certain pertinent details. de Oliveira-Garcia et al. (2002) reported

TABLE 3 | Virulence and virulence associated factors in *S. maltophilia* and its potential application in diagnosis/therapy.

Virulence and virulence associated factors	Unique composition/ structure/attributes	Virulence mechanisms	Potential application of the factor in diagnosis/therapy	Reference
Biofilm	*Coded for, by biosynthetic genes <i>rmlA</i> , <i>rmlC</i> , and <i>xanB</i> *Produced as the bacteria spread and intimately attach to surfaces	*Protects the bacteria against host immune factors *Promotes antibiotic resistance	Iron-restrictive regulation to slow done biofilm formation and reduce spread	Di Bonaventura et al., 2004; Huang et al., 2006
Quorum sensing	"Diffusible Signal Factor (DSF) quorum sensing (QS) system to"	"Mediate intra- and inter-specific signaling and regulate virulence-related processes"	Quorum quenching therapeutic approach by incorporating the structural analogs of DSF and other factors	Tay and Yew, 2013; Thomas et al., 2014; Huedo et al., 2015
Extracellular enzymes	"DNase, RNase, arbutinase, protease (StmPr1 serine protease) acetase, esterases, lipases, mucinase, acid and alkaline phosphatases, hyaluronidase, phosphoamidase, elactase, leucine arylamidase, and β -glucosidase"	*Utilizes varieties of enzymes to digest tissue proteins and serum making leading to the collapse of immune architecture, lesion, and hemorrhage	Synthesis of a Structural analogs of DSF to block extracellular enzymes production & other virulence factors	Crossman et al., 2008; Thomas et al., 2014; DuMont and Cianciotto, 2017
Flagella	Sequence identity to the flagellin of <i>Proteus mirabilis</i> , <i>Serratia marcescens</i> , <i>Escherichia coli</i> , etc.	*Facilitates evasion via motility from lysin, agglutinin, precipitin etc in humoral responses *Adhesins factor	Anti-Flagella antibodies	Zgair and Chhibber, 2011; Haiko and Westerlund-Wikström, 2013
Pili/fimbriae	"Fimbrillar structures (5–7 μ m in width) just like pili interconnecting bacteria and mediating adhesion of the bacteria to the abiotic surface"	*The aid in adherence, autoaggregation, colonization of surfaces, and *Antibiotic resistance	"Specific antibodies against SMF-1 fimbriae inhibited the agglutination of animal erythrocytes, adherence to HEp-2 cells and biofilm formation by <i>S. maltophilia</i> "	de Oliveira-Garcia et al., 2002, 2003
Small colony variant	Down-regulation of the bacterial electron transport and/or dihydrofolate reductase (DHFR) pathway sulfamethoxazole resistance, bringing about small colonial form	Switch to the SCV phenotype is a response to antibiotic pressure due to down-regulation of the bacterial electron transport and/or dihydrofolate reductase (DHFR) pathway	"SCV <i>S. maltophilia</i> from the sputum of CF patients has implications in laboratory testing"	Anderson et al., 2007

*Indicates particular concern.

the observation of appreciable sequence identity to the flagellin of *Proteus mirabilis*, *Serratia marcescens*, *Escherichia coli*, and others. in *S. maltophilia* flagella by analysis of N-terminal amino acid sequence. The bacteria are sometimes unflagellated, biflagellated or multiflagellated. Monopolar flagella arrangement in *S. maltophilia* using Leifson flagella stain is shown in **Figure 2**. *S. maltophilia* attach to abiotic surfaces and colonizes medical devices where it subsequently will form part of a biofilm (Elvers et al., 2001). This biofilm facilitates their attachment to cultured airway epithelial cells (de Abreu Vidip et al., 2001; de Oliveira-Garcia et al., 2003; Di Bonaventura et al., 2007) and their spread in an abiotic environment is facilitated by the flagella (Krzewinski et al., 2001). Both the biofilm production coded for, by biosynthetic genes *rmlA*, *rmlC*, and *xanB* and flagella are important in colonization and motility (Huang et al., 2006). This can be studied easily in the laboratory. *S. maltophilia* biofilms were analyzed by employing "in vitro tissue-culture assays." Scanning electron micrograph of a *S. maltophilia* biofilm cultured in a flow cell is depicted in **Figure 2D** (Briandet et al., 2008). The biofilm contributes to bacterial virulence as it protects the bacteria against antibiotics (Monroe, 2007; Hunter, 2008; Abraham, 2016) (See **Table 3**). *S. maltophilia*, like other

Gram-negative bacteria, utilizes the QS to coordinate expression of phenotypes and cell-to-cell communication, interlinked by QS molecules and receptors that depend on the number of cells present (LaSarre and Federle, 2013). *S. maltophilia* K279a genome further bears a diffusible signal factor (DSF) dependent QS system (Fouhy et al., 2007). This system was first detected in *Xanthomonas campestris* pv. *campestris* (Fouhy et al., 2007; Huang and Wong, 2007). DSF synthesis depends on *rpfF* within *rpf* operon to regulate virulence factors (Huedo et al., 2014). Two pathways of QS regulations include: N-Acyl homoserine lactones (AHLs) and Diffusible Signal Factor quorum sensing (DSF-QS). The synthesis and expression of DSF-QS pathway of *Xanthomonas*, *Xylella fastidiosa*, and in *S. maltophilia* require *rpf* gene cluster. DSF-QS regulates bacterial motility (Newman et al., 2004; Huedo et al., 2015; Suppiger et al., 2016), biofilm formation (Huedo et al., 2014; Garcia et al., 2015), and virulence (Huedo et al., 2014, 2015). *S. maltophilia* utilizes the interactions to coordinate phenotypes of the cells for host colonization and pathogenesis.

The development of small colonial form or small colonial variants (SCV) phenotype in *S. maltophilia* (**Figure 2B**) is a response toward reducing the antibiotic pressure on the

bacteria due to down-regulation of the BET (“bacterial electron transport”) and/or DHFR (“dihydrofolate reductase pathway”) (Table 3). *S. maltophilia* is also endowed with a number of enzymes which play vital roles in their pathogenesis. Some of them include deoxyribonuclease, protease, ribonucleases, among others as depicted in Table 3 (Windhorst et al., 2002; Nicoletti et al., 2011). Windhorst et al. (2002) describes the *StmPr1* protease from *S. maltophilia* that possess intracellular human tissue degradative potential. This *StmPr1* protease remains a notable pathogenicity factor in the bacteria targetable for the development of therapeutic agents (Windhorst et al., 2002; Nicoletti et al., 2011).

Another typical regulator is the c-di-GMP [“bis (3',5')-cyclic diguanosine monophosphate”], which is a cellular second messenger known for regulating bacterial activities like pathogenicity. The regulatory function of c-di-GMP in *S. maltophilia* remains unclear. In nosocomial *S. maltophilia*, *BsmR* is a negative regulator of biofilm development that degrades c-di-GMP. When *BsmR* are increasingly released, bacterial cells swim away (use their flagella) and are less likely to form quorum or biofilm (Liu et al., 2017). This is because *BsmR* regulates the expression of 349 genes including those for the expression of flagella genes. This involves *FsnR*, which “triggers” transcription of 2 flagellum-associated operons through adherence with their promoters (Kang et al., 2015). Certain pathways leading to the formations of essential macromolecules are regulated by the expression of small RNAs. Small RNAs are interconnected with QS and c-di-GMP to control bacterial physiology in the rhizosphere where *S. maltophilia* is a regular resident. These regulatory factors are potential targets for novel antibacterial agent against these bacteria.

As stated, the bacteria behave as a true pathogen in some cases (Kim et al., 2002; Hansen, 2012). This is reflected in their ability to infect immunocompetent individuals. Thomas et al. (2010) reported that the bacteria is an aetiologic agent for pyomyositis in an immunocompetent adult. Earlier, Pruvost et al. (2002) also described a case of community-acquired superficial pyoderma due to these bacteria in an immunocompetent host. It is also reported in other immunocompetent patients having community-borne meningitis together with plantar pyoderma (Libanore et al., 2004). Similar observation has been where *S. maltophilia* is prominent among pathogens in polymicrobial infections (Meyer et al., 2006). It shows the dual nature of this Gram-negative rod bacteria and the need to handle it as potential pathogen even when isolated from environment as commensal.

The risk of *S. maltophilia* infection are on the rise due to factors like prolonged hospitalization in an intensive care unit, HIV infection, cancer, cystic fibrosis, neutropenia, presence of surgical wound, artificial respiration, and previous administration of broad-spectrum antibiotics. Administering broad-spectrum antibiotics to which *S. maltophilia* has inherent resistance eradicates wide range of bacteria that would have restricted the colonization of tissues by *S. maltophilia* through microbial antagonism.

It is worth to briefly mention the *S. maltophilia* relationship with *Vermamoeba vermiformis* for growth and protection in the amoeba's which was investigated by Cateau et al. (2014) over

28 days under harsh conditions. This internalization ensures survival in hospital water systems and potentiate reinfection of patients (Cateau et al., 2014). Transmission electron microscopy images of *V. vermiformis* infected by *S. maltophilia* is illustrated in Figure 2E, where the arrow in this figure indicate the *S. maltophilia* inside the *V. vermiformis*.

DIAGNOSIS AND IDENTIFICATION FOR RESEARCH AND CLINICAL PURPOSES

A correct diagnosis is important in choosing appropriate therapy (Preud'homme and Hanson, 1990). The main challenge confronting proper diagnosis (and even control) of *S. maltophilia* in most clinical manifestation is absence of patient history due to initial rarity (Das et al., 2009). Therefore, misdiagnosis of the *S. maltophilia* cases for other possible etiologies often lead to development of fatal complications (Burdge et al., 1995). In a number of cases, the prescription of prolong antibiotic therapy interfere with non-specific immunity, resulting in a rapid colonization (Mamedova and Karaev, 1979; Drancourt et al., 1997; Agvald-Ohman, 2007). Addressing the presence of the organism in sputum as infection and subsequent use antibiotic therapy seem to be a wrong approach, since this might not translate to tissue colonization. A proactive diagnostic approach is needed before antibiotic therapy.

S. maltophilia has been miss-identified as *B. cepacia*-complex (Burdge et al., 1995; McMenamin et al., 2000). Conventional cultural methods on nutrient agar support the growth, although certain strains require methionine (O'Marley, 2009; Pinot et al., 2011). Isolation from natural sources (Pinot et al., 2011) including inanimate colonization or animal sources can easily be done with MacConkey agar supplemented with imipenem antibiotic. The imipenem inhibits many other bacteria (Rodloff et al., 2006). In addition, VIA-medium which contain Vancomycin, Imipenem, and Amphotericin B and mannitol agar base has been shown to be effective in isolation and recovery (Foster et al., 2008; Pinot et al., 2011). Further characterization on the small Gram negative, oxidase negative rod can be done using the Analytic Profile Index, API 20E and BD Phoenix (Becton Dickinson, France) systems (Aydemir et al., 2008). Biochemical/growth characteristics for phenotypic identifications are summarized in Table 1. Since API identification may not be totally accurate, speciation can be confirmed using molecular techniques such as genus-specific and specie-specific hybridization (Kempf et al., 2000; Cottrell et al., 2005). *In vivo* studies is also used and these studies utilize lipid peroxidation, lactate dehydrogenase activity and histopathological examination of tissue homogenate to measure the effect of *S. maltophilia* on tissue (Naika et al., 2004; Ibrahim and Nassar, 2008). If appropriate methods are used, the interference of the *S. maltophilia* infection in some body function can easily be studied. For instance, the improvement in laboratory identification brought about the recognition of Sm association in lung function in cystic fibrosis, though the organism was not expected in this particular case before its isolation (Goss et al., 2004).

Reference laboratories employ back-up methods and tools like “Matrix-assisted laser desorption/ionization time of flight” (MALDI-TOF), protein electrophoresis, polymerase chain reaction (PCR), DNA sequencing, transmission and scanning electron microscopy, immunological assay, western blotting, and N-terminal amino acid sequence analysis to confirm the identity of the organism (de Oliveira-Garcia et al., 2003; Chibber et al., 2008; Lira et al., 2012; Mukherjee and Roy, 2013; Adegoke and Okoh, 2015). The genetic make-up is determined using randomly amplified polymorphic DNA PCR (Krzewinski et al., 2001). A PCR (“polymerase chain reaction”) with total sensitivity and specificity approach emerged for *S. maltophilia* two decades ago (Whitby et al., 2000). Pulsed field gel electrophoresis (PFGE) technique (Denton and Kerr, 1998) is employed for typing during the molecular epidemiological study of *S. maltophilia*. Adamek et al. (2011) attempted using rep-PCR fingerprinting and partial *gyrB* gene sequencing to further characterize *S. maltophilia* within the same species, which though was not perfectly concluded, yet it was a promising pathway to understand the links between the clinical and environmental strains.

The MALDI-TOF, usually coupled as MALDI-TOF MS (“matrix-assisted laser desorption/ionization time-of-flight mass-spectrometry”) is a fast rising technology for high-throughput and quick microbial taxonomy. Rahi et al. (2016) affirmed that MALDI-TOF MS has relatively higher accuracy, a comprehensive database and is low-cost compared to other techniques for microbial identification and that the method is now replacing several others in clinical diagnosis. Also, PFGE with modifications is preferentially recommended to other established protocols in tracking *S. maltophilia* nosocomial outbreak due to its speed, simplicity, and cost effectiveness (Shueh et al., 2013).

In order to reduce method based error, Clinical and Laboratory Standard Institute (CLSI) recommended “Standard Broth Microdilution (SBM), a dried-down form of broth microdilution (DMD), E-Test (ET), agar disk diffusion (DD) e.g., with interpretive manuals displayed in **Table 4**, and agar dilution (AD)’ methods. These methods are of importance for studies of antibiotic susceptibility testing (AST) of *S. maltophilia* with Trimethoprim/Sulfamethoxazole (Wiles et al., 1999), and these methods are also used to provide epidemiology work-base data for use in perspective Sm-control arsenal. Standards “zone diameter and minimal inhibitory concentration (MIC) interpretive Standards’ for *S. maltophilia*” as approved by Clinical and Laboratory Standards Institute (2014) is depicted in **Table 3**.

INFECTION PROGNOSIS AND/OR THERAPEUTIC OUTCOME

There is an increased risk of co-infection that affects the limited the therapeutic option for *S. maltophilia*. Prognostic factors that include therapy-based immunosuppression, blood-based carcinoma, neutropenic, transplantation etc. are also important to determine recovery or mortality, resulting from *S. maltophilia*. Conditions that remove myelosuppression and invasive indwelling catheter, and prompt treatment with

TABLE 4 | Zone diameter and Minimal Inhibitory Concentration (MIC) interpretive standards for *Stenotrophomonas maltophilia* (M100-S24, Clinical and Laboratory Standards Institute, 2014).

Test/ Report group	Antimicrobial agent	Disk content	Zone diameter interpretive criteria (nearest whole mm)			MIC Interpretive Criteria (μg/mL)		
			S	I	R	S	I	R
β-LACTAM/β-LACTAMASE INHIBITOR COMBINATIONS								
B	Ticarcillin-clavulanate	-	-	-	-	≤16/2	32/2-64/2	≥128/2
CEPHEMS (PARENTERAL) (INCLUDING cephalosporins I, II, III, and IV)								
B	Ceftazidime	-	-	-	-	≤8	16	≥32
TETRACYCLINES								
B	Minocycline	30 μg	≥19	15-18	≤14	≤4	8	≥16
FLUOROQUINOLONES								
B	Levofloxacin	5 μg	≥17	14-16	≤13	≤2	4	≥8
FOLATE PATHWAY INHIBITORS								
A	Trimethoprim-sulfamethoxazole	1.25/23.75 μg	≥16	11-15	≤10	≤2/38	-	≥4/76
PHENICOLS								
B*	Chloramphenicol	-	-	-	-	≤8	16	≥32

*Not routinely reported on isolates from the urinary tract.

pre-confirmed antibiotic have been reported to determine the chance of recovery (Vartivarian et al., 1994) as their surfaces have been observed to enhance colonization. Johnson (2000) noted that nearly all mucocutaneous complications involving *S. maltophilia* of HIV infected individuals either improved or were resolved if restoration of immune function is achieved by highly active antiretroviral drugs.

Primary cellulitis, disseminated cutaneous nodules, and mucocutaneous ulcers caused by *S. maltophilia* are often associated with underlining malignancies. Some complications of *S. maltophilia* infection accompanied with metastatic skin nodules and/or systemic inflammatory response syndrome (sepsis), muco-cutaneous infections in neutropenic patients with cancer have poor prognosis. Marchac et al. (2004) stated that *Aspergillus fumigatus* co-infect individuals with *S. maltophilia*. The report suggested that the effect of *A. fumigatus* co-infection with *S. maltophilia* has no association with administration of steroid. In the words of Marchac et al. (2004) “allergic bronchopulmonary aspergillosis was diagnosed in 5 of 17 (30%) patients with *A. fumigatus* in the sputum and taking oral steroids.”

High mortality often resulting from mucocutaneous *S. maltophilia* infections in neutropenic patients with cancer makes the effect of secondary immunosuppression a worrisome trend in the infection prognosis (Tseng et al., 2009; Wakino et al., 2009; Freifeld et al., 2011; Piena et al., 2015). Accompanying widespread injury to vital somatic tissues might be a relative factor to this. Clinical effort to reduce alarming mortality rate from various forms of this bacterial infection and its attending complications is imperative. For instance, *S. maltophilia* is increasingly recognized among the cancer patients and the

mortality brought about by the organism in the cases of bacteremia in non-burned patients was reported as 10–69% (Micozzi et al., 2000; Friedman et al., 2002; Senol et al., 2002). Tsai et al. (2006) reported a mortality rate of 30.7% in burn patients colonized by *S. maltophilia* while all (100%) the patients that acquired nosocomial meningitis involving *S. maltophilia* died (Yemisen et al., 2008).

CONTROL OF *S. MALTOPHILIA*

Since *S. maltophilia* both act as an opportunistic pathogens and has been implicated among immunocompetent individuals (Kim et al., 2002; Pruvost et al., 2002; Libanore et al., 2004; Thomas et al., 2010; Huang et al., 2013; Wang C. H. et al., 2014; García-León et al., 2015; Reynaud et al., 2015), its control is quite essential. Removal of the invasive indwelling devices without change of medication, hygienic handling of breached skin or self-fix medical devices and proper quality control measure in the preparation of irrigation solution or intravenous fluid are imperative in the control and management of nosocomial *S. maltophilia* infection. Elsner et al. (1997) observed that a patient with fatal pulmonary hemorrhage, acute leukemia, and fulminant pneumonia recovered immediately after an indwelling contaminated catheter was removed, affirming the role of such devices in *S. maltophilia* infection. While considering principles of catheter related infection (CRI), Mer (2005) also reported that, as a general rule the removal of catheter in catheter-related

blood stream infections (CRBSI) is compulsory and that most of the infectious complications usually resolve after removal of the catheter.

ANTIBIOTIC ADMINISTRATION

Treatment of infection caused by *S. maltophilia* is complicated because this pathogen exhibits multi drug resistance (MDR). Worse still, the environmentally isolated strains also showed this MDR as depicted in **Figure 3**, limiting the available therapeutic options (Denton and Kerr, 1998; Köseoglu et al., 2004) if infection occurs. This is worsened by co-infection, which makes the treatment of *S. maltophilia* more cumbersome. *S. maltophilia* exhibits multiple resistance against antibiotics suitable for treating nosocomial infections. It is imperative to remember that some of the antibiotics used in the treatment of ESBL producers like *S. maltophilia* are broad spectrum. Hence, utmost care needs be taken in its selection, as consideration to patient's ability to withstand drug contra-indication(s) is imperative even in some polymicrobial cases. Abuse of the extended spectrum antibiotics may lead to selection of highly resistant *S. maltophilia* strains. Co-trimoxazole (trimethoprim-sulphamethoxazole, TMP-SMX) is the treatment of choice in symptomatic infection but no available information exists on the best management of co-trimoxazole-resistant infections.

Ciprofloxacin and other older quinolones reportedly possessed 50% efficacy against *S. maltophilia in vitro* (Denton

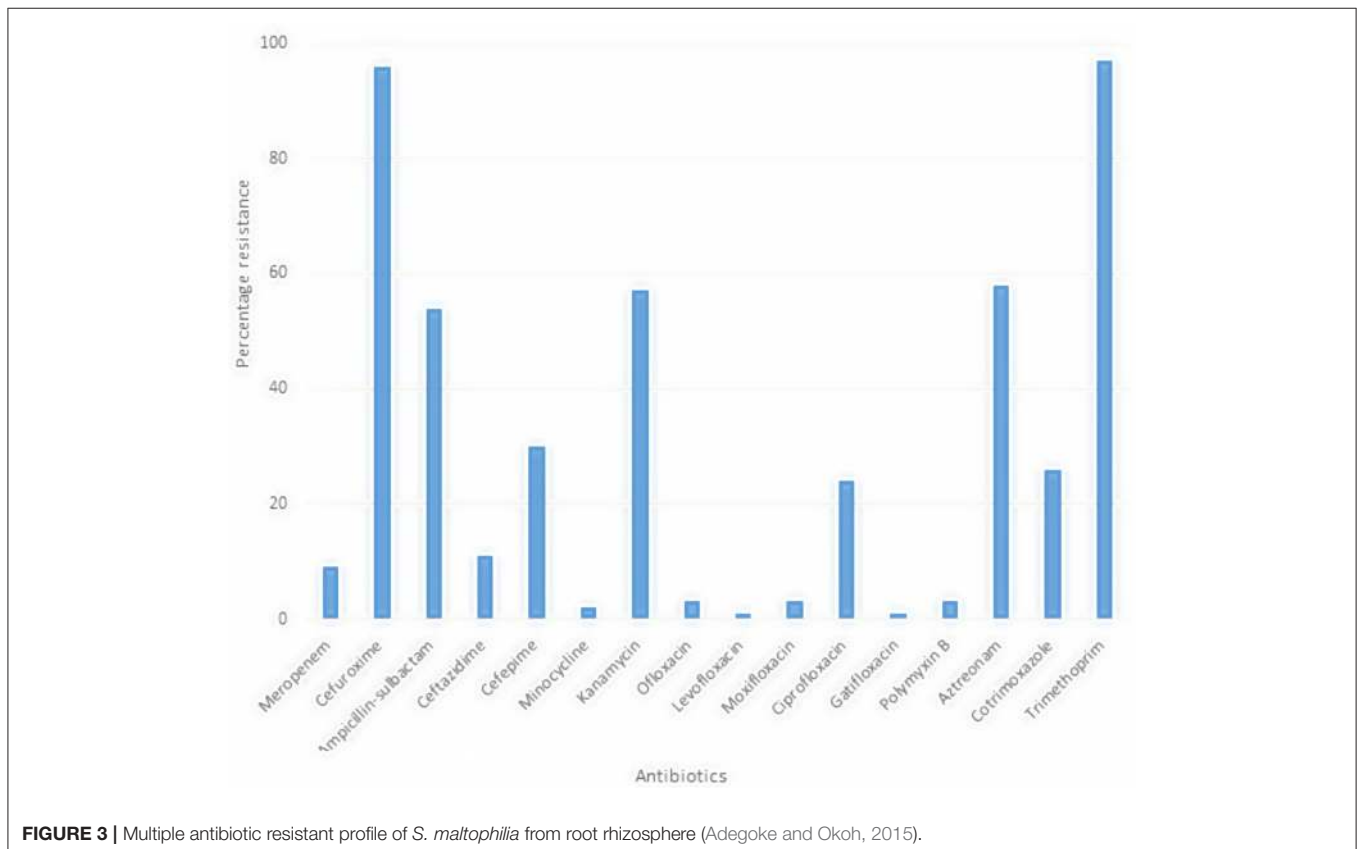


FIGURE 3 | Multiple antibiotic resistant profile of *S. maltophilia* from root rhizosphere (Adegoke and Okoh, 2015).

and Kerr, 1998). Observation was also made by Weiss et al. (2000) that trovafloxacin, clinafloxacin, and morrifloxacin have appreciable *in vitro* activity against the organism and have been employed to treat chronic infections by it. Trimethoprim—sulphamethoxazole, TMP-SMX have been recommended by a number of researchers as initial therapeutic option for serious *S. maltophilia* infections (Lo et al., 2002). Fluoroquinolone was reported as better therapeutic choice in case of cystic fibrosis, as it has much higher peak lung concentration than peak plasma concentration (Schubert et al., 2005). However, exploiting the benefit of synergy in combination therapy using the fluoroquinolone antibiotics or TMP-SMX have several advantages, due to the ease with which the organism acquires resistance to monotherapy (Weiss et al., 2000; Foo et al., 2002). Zelenitsky et al. (2005) reported better bactericidal kinetics due to combination therapy involving TMP-SMX and ceftazidime than for monotherapy. A study by Wang Y. L. et al. (2014) showed that clinical success rates monotherapy with fluoroquinolone and TMP-SMX were 52 and 61% respectively ($P = 0.451$). Therapeutic successes have also been reported with the use of minocycline (MIN) and doxycycline (DOX) (Chung et al., 2013; Farrell et al., 2014). They were specifically recommended for being most potent antibiotics against *S. maltophilia* isolates (MIN = 98.9%, DOX = 94.6%) compared to TMP-SMX of 93.4% in the Esposito et al. (2017) study. Though *S. maltophilia* is known for resistance to imipenem and other antibiotics with lower spectrum than imipenem, any of TMP-SMX, MIN, or DOX can still be good choice for treatment, following appropriate AST.

Even then, secondary drug interaction with body metabolism when considering appropriate therapy for *S. maltophilia* is imparative. Some effective antistenotrophomonad drugs without damaging primary contra-indications might interfere with other existing drugs in plasma (Dickinson et al., 2001). Carbapenem antibiotics with estrogen affect the effectiveness of contraceptive *in vivo*. Some patients' intolerant of TMP-SMX should be noted (Archer and Archer, 2002). Dalamaga et al. (2003) reported improvement in the *S. maltophilia* infection treatment in burn patients following the administration of TMP-SMX. Careful consideration is expected before antibiotic regimen is prescribed in *Stenotrophomonas* control arsenal. Tesoro et al. (2011) recommended co-trimoxazole-ticarillin-clavulanate combination therapy due to their synergism and the reported bactericidal effect against the ticarcillin-clavulanate resistant strains. This should be considered for the patients who are TMP-SMX tolerant.

BASIS OF RESISTANCE

S. maltophilia exhibits high AR profile due to both inherent and acquired antibiotic resistant genes (Alonso et al., 2004; Di Bonaventura et al., 2004; Nicodemo and Paez, 2007; Gilbert et al., 2010). It is important to note that, DSF-QS earlier discussed also regulates AR (Fouhy et al., 2007). Besides this, all *S. maltophilia* strains have been shown to harbor resistant genes (Alonso et al., 2004; Nicodemo and Paez, 2007; Gilbert et al., 2010). This implies that resistant strains to quinolones, cotrimoxazole

(TMP-SMX), cephalosporins-antibiotics and other conventional therapy for *S. maltophilia* infections are upcoming. In a Canadian hospital environment for instance, erythromycin and tetracycline resistance genes were detected in 100% air samples collected (containing *S. maltophilia*) from hospital rooms, (Furushita et al., 2003; Perron et al., 2015). In Korea, Song et al. (2010) observed that antibiotic resistance gene (ARGs) *sul1* within class 1 integrons rather than *sul2* were responsible for TMP-SMX resistance. In *S. maltophilia*, isolates can be linked to multiple ARGs also within the Class 1 integrons. ARGs, macrolide phosphotransferase (mphBM) amidst cluster of genes (like heavy metal tolerance gene) cadmium efflux determinant (*cadA*) as well as its transcriptional regulator gene (*cadC*) was reported in *S. maltophilia* D457 by Alonso et al. (2004). In the study, the *S. maltophilia* (a Gram-negative) acquired ARGs from gram-positive bacteria. Similarly, the role of *S. maltophilia* efflux pumps (*EfPs*) ABC, DEF, GH, IJK, MN, OP, VWX, and YZ multidrug efflux pump cannot be overlooked. This is because it nurtures the innate multidrug resistance (MDR) in *S. maltophilia* (Zhang et al., 2001, 2004; Li et al., 2002; Sánchez et al., 2002; Crossman et al., 2008; Gould et al., 2013; Huang et al., 2013; García-León et al., 2015). This is outlined in **Table 3**. Zhang et al. (2001) noted that *S. maltophilia* efflux pump F, *SmeF* in a hyper-expressed form and multidrug efflux components could enhance MDR in *S. maltophilia*. The MDR clinical isolate of *S. maltophilia* strain was also reported to effect the over-expression of the resistance-nodulation-division (RND) family efflux pumps *SmeZ* and *SmeJK* (Gould et al., 2013). The RND-type *EfPs* *SmeABC* in *S. maltophilia* is under the control of two-component system (TCS) known as *SmeRS*, situated above the efflux pump genes. Studies showed that if *SmeR* response regulator are denatured, AR would reduce and overexpression of *SmeR* triggers up the expression of *smeABC* (Li et al., 2002). The expression of *AME* gene cassettes predicates increased resistance to aminoglycoside (Huang et al., 2015). The chromosomal aminoglycoside resistance determinants also known as aminoglycoside-modifying enzymes (AMEs) are born by *AME* genes, which in turn are the predominant gene cassettes resident in the class 1 integrons of *S. maltophilia*. All the attributes of these bacteria give further credence to the need to incorporate isolates like *S. maltophilia* and *Acinetobacter* species as test isolates in drug research as proposed by Adegoke and Okoh (2012).

While inactivating enzymes and efflux pumps are recognized, yet in-depth studies are still on-going in this area. Mutant library accounted for extensive unusual AR mechanisms and it encompasses genes for metabolism, and resistant phenotypes. Inducible beta-lactamase activity (“2 chromosomally encoded-lactamases, *L1* and *L2*, and an aminoglycoside acetyltransferase”) (see **Table 5**) (Poole, 2001), poor outer membrane permeability and efflux mechanism (McKay et al., 2003), horizontal gene transfer (HGT) (Alonso et al., 2004), biofilm formation, extracellular slime, or glycocalyx are important factors in multiple AR (Di Bonaventura et al., 2004). Furushita et al. (2005) observed inter-cluster divergence in beta lactamase gene in six strains of *S. maltophilia*, suggesting horizontal gene transfer (HGT) among them. Therefore, ARGs are of specific interest due

TABLE 5 | Some of the resistance genes acquired/reserved in *S. maltophilia*.

Antibiotic resistance genes	Expression	Antibiotic/antibiotic group affected	References
<i>L1</i>	Beta lactamase production	Beta lactam antibiotics	Zhang et al., 2000; Avison et al., 2002; Hu et al., 2008; Lin et al., 2009
<i>L2</i>	Beta lactamase production	Beta lactam antibiotics	Zhang et al., 2000; Avison et al., 2002; Hu et al., 2008; Lin et al., 2009
<i>Sul1</i>	Sulphonamide hydrolases' production	Sulphonamides/trimethoprim-sulfamethoxazole	Toleman et al., 2007; Wang Y. L. et al., 2014; Adegoke and Okoh, 2015
<i>Sul2</i>	Sulphonamide hydrolases' production	Sulphonamides/trimethoprim-sulfamethoxazole	Toleman et al., 2007; Wang Y. L. et al., 2014; Adegoke and Okoh, 2015
<i>Sul3</i>	Sulphonamide hydrolases' production	Sulphonamides/trimethoprim-sulfamethoxazole	Wang Y. L. et al., 2014; Adegoke and Okoh, 2015
"Sme	<i>ABC</i>	Efflux pump (RND based)	Ciprofloxacin/floroquinolone, tetracycline
	<i>DEF</i>		Meropenem, chloramphenicol
	<i>GH</i>		Undetermined
	<i>IJK</i>		Tetracycline, aminoglycosides, ciprofloxacin
	<i>MN</i>		Undetermined
	<i>OP</i>		Aminoglycosides, macrolides, doxycycline, some quinolone
	<i>WX</i>		quinolone
	<i>YZ"</i>		Aminoglycosides
<i>Smqnr</i>	Penta-peptide repeat protein	Quinolone	Sánchez and Martínez, 2009; Zhang et al., 2011; 2012
Bacterial topoisomerase and gyrase genes	Chromosomal mutations of the quinolone resistance-determining regions in DNA gyrase and DNA topoisomerase IV	Quinolone and fluoroquinolone	Jia et al., 2015; Kanamori et al., 2015
<i>spgM</i>	Phosphoglucomutase	ceftazidime, gentamicin, nalidixic acid, piperacillin-tazobactam, polymyxin B, polymyxin E, ticarcillin-clavulanic acid, vancomycin	Liaw et al., 2010

to the transferability from one species to another (Alonso et al., 2004).

These aforementioned resistance attributes are common to both environmental and clinical strains (Botes et al., 2007; Youenou et al., 2015). It evidenced their strong similarities in possible attributes for host invasion as well as antibiotic resistance (Alavi et al., 2014; Youenou et al., 2015). *S. maltophilia* can acquire and transfer the ARGs to other bacteria species through HGT (Berg et al., 2005, 2016) in the root rhizosphere of plants

SUGGESTION FOR TACKLING THE GROWING HEALTH THREAT FROM *S. MALTOPHILIA*: FUTURE TREATMENT

S. maltophilia must be accepted as true pathogen due to its high pathogenic potentials it possesses (Alonso et al., 2004; Nicodemo and Paez, 2007; Gilbert et al., 2010; Huang et al., 2013; Wang C. H. et al., 2014; García-León et al., 2015; Reynaud et al., 2015). Since the rhizospheres' strains in Brazil was the same as the clinical etiology of infection in Australia and Spain (Youenou et al., 2015), the organism no doubt is an emerging threat (Huang et al., 2013; Wang C. H. et al., 2014; García-León et al., 2015; Reynaud et al., 2015), either from clinical settings or in the root

rhizosphere. Adegoke and Okoh (2015) reported high resistance and detection of resistance genes among *S. maltophilia* from root rhizosphere, making it potentially difficult to threat if it infects an organism. It has even been reported that the bacteria have higher competitive advantage in root rhizosphere than most known phytopathogens, making its presence an advantage to plant (Cernava et al., 2015). This gives the *Stenotrophomonas* a competitive advantage among phytopathogens in the rhizosphere and makes it potentially bacteria for internalization into plants, though as plants' growth promoter (Miceli et al., 2015). This scenario posits the bacteria as a threat in human body system, making microbial antagonism (a form of natural immunity produce by body microflora) ineffective.

Based on report of studies on *Staphylococcus aureus* and *Acinetobacter baumannii* by Su et al. (2011) and Davies and Marques (2009), the right approach is by blocking the virulence factors in *S. maltophilia* to prevent further colonization in infection state and to resensitize antibiotics, to which such factors have rendered ineffective. Interfering with bacterial communication can potentially prevent progression of infection (Cegelski et al., 2008). This QS disruption is one of the novel approach to tackle bacterial infections (Alanis, 2005; Su et al., 2011) and inhibition of biofilm formation by 2-Aminoimidazole have been reported by Žula et al. (2013), and 2-bromoalkanoic

acids reported by Gutierrez et al. (2013). Meanwhile Davies and Marques (2009) had earlier reported disruption of *S. aureus* biofilms using 10 nM of cis-2-decenoic acid. Another researcher, Su et al. (2011) reported that higher biofilm dispersing potential associated with Pb-compounds than the natural compound, cis-2-decenoic acid. They were also reported to doubly to quadruply re-induce MRSA resistance to oxacillin. More clinical based research in biofilm inhibition, QS disruption and blockings other virulence factors (**Table 3**) as it relates to *S. maltophilia* are hereby recommended.

As stated earlier, *S. maltophilia* should also be included as one of the test isolates in antibacterial drug research as we proposed previously (Adegoke and Okoh, 2012). Limited antibacterial drug studies have ever considered these bacteria as test isolates. There should be consideration for its alarming resistance to many of the existing antibacterial drugs, in the last line of defense (e.g., imipenem) and the reports showing the organism as a repository of ARGs (Crossman et al., 2008; Gould et al., 2013; Huang et al., 2013; Adegoke and Okoh, 2015; García-León et al., 2015). The outcome of the study that reported high effectiveness of Epigallocatechin-3-gallate (EGCG) from green tea (Gordon and Wareham, 2010), essential oil (Fabio et al., 2007), nanoemulsions, peptide inhibition of beta lactamase or the use of appropriate protease inhibitor and use of cationic compounds should be incorporated in *Stenotrophomonas* control arsenal. An example is cationic peptides extracted from amphibians, which allow material absorption by *S. maltophilia* as it increases the outer membrane permeability of *S. maltophilia* (**Figure 1**). These peptides are usually more potent than conventional (Kraus and Peschel, 2006). The EGCG from green tea has been reported to interfere with *S. maltophilia* biofilm production as well as reduces their cell count *in vivo* (Vidigal et al., 2014). Using confocal laser scanning microscopy, Vidigal et al. (2014) observed huge increase in dead cell within the biofilm produced by the bacteria in cystic fibrosis patients based on the EGCG dosage used. The studies show success in both *in-vitro* and *in-vivo* application and may be a novel therapeutic alternative to solve the problems associated with drug resistance. Current fluoroquinolone therapy is known with severe contra-indication in children and pregnant women (Larsen et al., 2001), emphasizing the need for more antibacterial research with the bacteria in focus. Prospective

anti-*Stenotrophomonas* drugs should target the *Stmpr1* protease known to have indispensable function in its virulence (Windhorst et al., 2002; Nicoletti et al., 2011).

Lysogenic phase as well as lytic phase of *Stenotrophomonas* strains with phages have been demonstrated, showing the possibilities of employing bioengineered bacteriophage therapy in the control of multiple antibiotic resistant *Stenotrophomonas* infection (Hagemann et al., 2006; García et al., 2008; Vos et al., 2009). A number of promising phages that can serve as therapeutic alternatives to *S. maltophilia* are emerging (Liu et al., 2013; Lee et al., 2014; Peters et al., 2015) and listed in **Table 6**. Phages DLP1 and DLP2 were observed by Peters et al. (2015) with potency of infecting wide host range of bacterial pathogens, including *S. maltophilia* and have been suggested as potential tool for possible phage therapy. Other bacteriophages have also been shown with such potentials. An example is the DLP6 (vB_SmoM-DLP6) which was hosted with *S. maltophilia* strain D1571 from soil. The phage DLP6 which belong to Myoviridae family infected and lysed about 50% of the tested clinical *S. maltophilia*, including the original *S. maltophilia* strain D1571 (Peters et al., 2017). This creates a vibrant roadmap for more promising phage therapy where several conventional antibiotics fail.

CONCLUSION

S. maltophilia has a very dynamic characteristic. The organism is not only an opportunistic pathogen in severe life threatening infection in the vulnerable but also reported as true pathogen in immunocompetent individuals. This bacterial species is accompanied with illnesses and death from RTI, especially in clinical conditions like cystic fibrosis, bacteremia and/or urinary tract infections among others. Appropriate diagnosis with adequate caution is imperative as arbitrary administration of antibiotic might result in increase in myelosuppression and/or selection of resistant strains of the species. *S. maltophilia* possesses inherent resistance to antimicrobials predicated by low outer membrane permeability, natural MDR efflux systems, and resistance mechanisms like the production of two inducible chromosomally encoded-lactamases. Imminent danger in *S. maltophilia* control arsenal should be avoided by reclassifying the organism as pathogen and incorporating it as

TABLE 6 | Some phages for potential treatment of multiple antibiotic resistant *S. maltophilia*.

Phages	Description	Source	Host/Host range	References
DLP1	Exhibits unique plaque development	Red Deer River sediment	Wide range	Peters et al., 2015
DLP2	Phage DLP2 is larger than DLP1. It has a non-contractile tail (≈ 205 nm; capsid size ≈ 70 nm in diameter)	soil planted with blue flax	Wide range	Peters et al., 2015
Maltocin P28	"It appears like a contractile but non-flexible phage tail (phage remnant) structure based on electron microscopy"	<i>S. maltophilia</i> strain P28	Due to the sequence analysis similar to P2 phage genome, it might have multiple host range	Liu et al., 2013
Smp131	Morphology resembles the members of myoviridae (genome size ≈ 250)	Clinical samples	Narrow host range	Lee et al., 2014
phiSMA5	Morphology resembles the members of myoviridae (genome size ≈ 160 kb)	clinical samples	Narrow range	Lee et al., 2014
ϕ SHP1	Filamentous phage	Environmental samples	SMP1 specific	Liu et al., 2012

one of the test isolates in antibacterial drug research. Strict adherence to rules of hygiene, quality control in hospitals units and pharmaceutical companies, avoiding the abuse of antibiotics etc. are advocated, as these conditions predispose the organism to antibiotic resistance. Antimicrobial resistance genes from the organism could be transferred to other species and cause serious public health concerns. Hence, the use of such genes as markers for genetically modified crops should be discouraged. The suggested therapeutic options in this article will surely lead a way forward in the *Stenotrophomonas* control arsenal.

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AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

We acknowledge the University of Fort Hare, National Research Foundation of South Africa and the South Africa Medical Research Council for financial support.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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