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A Critical Review of the Bacteria Serratia marcescens and its Impact on Human Health

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Abstract

Serratia marcescens is a gram negative bacterium of the family Enterobacteriaceae. *Serratia marcescens* is a motile opportunistic pathogen that produces the signature red pigment product prodigiosin. It possesses a thin cell membrane and thin peptidoglycan layer surrounded by an outer lipopolysaccharide (LPS) filled membrane. This saprophytic bacteria is able to withstand several different environmental conditions as it is a facultative anaerobe that can grow at temperatures ranging from 10ÂºC to 40ÂºC and at pH's ranging from 5 to 9 (Hejazi and Falkiner, 1997).

The Bacteria:

Serratia marcescens is a gram negative bacterium of the family Enterobacteriaceae. *Serratia marcescens* is a motile opportunistic pathogen that produces the signature red pigment product prodigiosin (See Figure 1). It possesses a thin cell membrane and thin peptidoglycan layer surrounded by an outer lipopolysaccharide (LPS) filled membrane. This saprophytic bacteria is able to withstand several different environmental conditions as it is a facultative anaerobe that can grow at temperatures ranging from 10ÂºC to 40ÂºC and at pH's ranging from 5 to 9 (Hejazi and Falkiner, 1997). It is due to these factors that *S. marcescens* is found in soil and water samples across many environments. Since this species of bacteria is able to thrive as a biofilm in aqueous environments or in its natural form in soil, it is also found in several species of plants, insects and animals. In addition to its natural existence in the environment, *S. marcescens* is a nosocomial pathogen that thrives in hospital environments and environments where levels of water and food sanitation (Especially meats and breads) are low (Mahlen, 2011).

Being classified as a nosocomial pathogen indicates that *S. marcescens* is a strain of bacteria that is able to thrive and infect humans in a hospital. It is known to cause several respiratory diseases such as pneumonia, central nervous system diseases, urinary tract infections, and bloodstream and wound infections (See Table 1). This is an opportunistic pathogen that primarily targets individuals who are immunocompromised; however, the contraction of this pathogen by health care workers and by non-hospital community areas occurs. Infrequently the contraction of this pathogen occurs due to contaminated surgical equipment, where gastrointestinal and respiratory tract infections are most frequently observed (Pitout, 2007).

Source of Outbreaks:

During the early 1900's, the dangers of *S. marcescens* were unknown, thus use of the correct safety measures when using this species were not implemented. This species of bacteria produces a distinct "blood like" protein that scientists often used it as a molecular marker to trace bacterial processes. Unfortunately, in many cases these individuals were infected with the pathogen, some resulting in death. Although the information on *S. marcescens* has drastically increased over the past century, the outbreak and spread of this bacterium still occurs. One source that contributes to the spread of this pathogen is the contamination of surgical equipment. The physical structures of the surface (Pili and hydrophobicity) of *S. marcescens* allow it to optimally bind to several surfaces, including an abundance of plastic-based surgical equipment (Fleisch *et al.,* 2002). This contributes to the spread of this pathogen to exposed individuals.

The other major source that contributes to the spread of this pathogen is the contamination of food or water sources generally due to unhygienic conditions. This species of bacteria is highly motile and able to withstand varying conditions. Without proper chlorination of water, this bacterium ultimately infects human populations. Infected meat products are also a source of infection to humans. These conditions are often seen in developing countries and therefore chances of outbreaks are highest in those areas (Hejazi and Falkiner, 1997). Although the chances of outbreak are high, the probability of transmission to a general population is low, therefore there has been no reported pandemic concerning *S. marcescens.* However, isolated epidemics have occurred often in hospital settings (Lewis *et al.,* 1989) and more specifically, neonatal intensive care units (Cristina,

2019).

Mechanism of Infection:

The amount of reported *S. marcescens* induced diseases has drastically decreased as information on this species of bacteria has increased. There are many structural factors that contribute to and increase the virulence of this species of bacteria. One of these structures is the presence of multiple pili. These pili extend from the surface of the cell membrane and allow for this organism to adhere to many surfaces including epithelial cells. Another factor that increases the pathogenicity of this species is the presence of many hydrophobic groups on the cell surface exterior. This results in the bacteria having a greater partitioning effect in highly hydrophobic oil like substances. Specifically this also allows the bacteria to adhere more strongly to plastic structures such as catheters and other surgical equipment (Hejazi and Falkiner, 1997).

Another major factor that contributes to the pathogenicity of this species is the lipopolysaccharide (LPS) containing outer membrane. The LPS layer has two major roles relating to virulence in which the Lipid A subunit is responsible for endotoxin activity and the oligosaccharide side chain confers partial resistance to certain antibiotics. The introduction of *S. marcescens* Lipid A into the human body results in an immunologic response in which this foreign antigen interacts with monocytes and macrophages. These immune response cells secrete several cytokines, including different groups of the interleukin (IL) and family tumour necrosis factor alpha (TNF-a). This then causes the production of endogenous inflammatory mediators and stimulates cellular toll-like receptors. This eventually leads to an overly active immune response in which the activity of the host cell defences ultimately exhaust and kill the cell (Makimura *et al.,* 2007).

Treatment:

Throughout the history of human infection involving *S. marcescens,* the use of several different antibiotics has been implemented to effectively kill this strain. Unfortunately the misuse of certain antibiotics has contributed to the resistance of this pathogen. S*. marcescens* has become resistant to many antibiotics such as penicillin and cephalosporin (See Table 2). This resistance has primarily occurred due to horizontal gene transfer, in which the uptake of a plasmid conferring antibiotic resistance is introduced into a genetically susceptible cell. Unfortunately, since the species of the donor DNA is not a limiting factor, preventing resistance is difficult to control. In addition to this genetically induced resistance, this strain contains an efflux pump and an LPS membrane layer that both effectively prevent foreign substances from entering the cell (Farrar and O'Dell, 1976).

While this species has gained resistance to several antibiotics, it is still susceptible to third-generation cephalosporins. Until the species developed resistance to gentamicin in the mid-1970s, aminoglycosides were the drug of choice for treatment. Coincident with the decline in use, aminoglycoside resistance has decreased by 6% amongst *S. marcescens* isolates (Lockhart, 2007). Additionally, this treatment causes damage to cell membrane integrity, as well as is nephrotoxic and ototoxic (Shakil *et al.,* 2008). As a result, these agents are largely used in combination with other antibiotics. Fluoroquinolones were able to effectively inhibit this species growth by inhibiting DNA gyrase activity. This effectively led to the fragmentation of bacterial DNA as torsional strains cannot be relieved effectively (Fabrega *et al.,* 2009). However, divergent rates of fluoroquinolone resistance have limited the use of these antibiotics in cases of serious infection. Fluoroquinolone administration has become restricted to uncomplicated infection at clinical sites where effective antibiotic concentrations are attainable and thus reduce the likelihood of development of resistance (Livermore, 1998).

Previously, third-generation cephalosporins (such as cefotaxime and ceftazidime) were the cornerstone of treatment. However, the recognition that *S. marcescens* can both engage in constitutive over-production of broad spectrum AmpC beta-lactamase as well as express a range of ESBLs, has reduced the use of third generation cephalosporins as empiric agents. The utilization of these agents in isolates with evidence of AmpC derepression is contentious. High-frequency selection of AmpC derepressed mutants is not commonly associated with *S. marcescens*. However, the likelihood of selection ultimately depends on the site of infection, bacterial population density, drugs availability at the site of infection and the condition of the patient. Thus, in urinary tract infections where the level of available antibiotic is sufficient and the potential for selection is reduced, the drug of choice remains third-generation cephalosporins, used solely or with aminoglycosides (Livermore,1998). More often, in isolates of *S. marcescens* with evidence of AmpC derepression and/or ESBL production, the drug of

choice is the carbapenems, as they remain active against bacteria with high levels of AmpC and ESBLS (Harris, 2012). However, carbapenemase-mediated resistance has emerged, suggesting careful administration be advised (Cai, 2008). In isolated outbreaks and sporadic episodes, reports of chromosomal and plasmid-mediated carbapenemase production have occurred thus making carbapenem treatment reserved for serious infection. If the pattern of spread of multi-resistant carbapenemase is reflected in this pathogen, treatment options will be severely limited (Cai, 2008).

S. marcescens employs virulence factors such as prodigiosin, proteases, biofilm and its ability to swim and swarm, all of which are controlled by a mechanism of intercellular communication termed quorum sensing. Quorum sensing enables bacterial cells to monitor their numbers and respond by coordinating the expression of genes including virulence genes. Due to the *S. marcescens high v* irulence and resistance, the risk of further development of additional antibiotic resistance is posed with administration of antibiotics during treatment. It is supposed that quorum sensing inhibition is one useful approach that can help in treating infections, without exerting stress on the growth of bacteria to avoid the evolution of antibiotic resistance (Abbas, 2018). Glyceryl trinitrate (GTN) is an anti-hypertensive that has anti-microbial properties (Abbas, 2016). GTN exerted antibiofilm activity against *Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa* and *Candida albicans*. Further, it has demonstrated inhibition of quorum sensing in *Pseudomonas aeruginosa* (Abbas 2016) as well as *S. marcescens* (Abbas, 2018). GTN demonstrated, by its ability to cause significant reduction in the production of the quorum-sensing regulated *violacein* pigment, a reduction in quorum sensing associated virulence factors. GTN showed a remarkable reduction in prodigiosin pigment (Figure 2), protease production (Figure 3), biofilm production and blocked swarming motility (Figure 4,5) (Abbas, 2018). An advantage of GTN treatment is that it is FDA approved which makes clinical application possible. As *Serratia marcescens* causes surgical wounds and urinary tract infections, GTN can be used topically or as a catheter lock solution, for catheter associated urinary tract infections (Galloway, 2012).

While these treatments are effective against individuals already afflicted by *S. marcescens*, prevention remains the greatest means of combating this pathogen. The best way to avoid any unintentional contact with this species is to ensure the proper sterilization and sanitation of equipment, location, food and water. A variety of disinfectants such as phenolic disinfectants, (1% sodium hypochlorite, 70% ethanol) or formaldehyde are all effective against *S. marcescens* and can effectively prevent residues of these bacteria from forming on surfaces. Equipment that is used in a hospital setting should also undergo autoclave treatment. Lastly, all food and water sources should be inspected regularly for any trace of bacterial contaminant. In addition to inspection, these products should be treated with appropriate sanitizing agents (Human Pathogen and Toxins Act, 2009).

Laboratory Use:

When working with different species of bacteria it is imperative to have a full understanding about the potential risks that these bacteria pose to humans. The Human Pathogens and Toxins Act (HPTA) aims to inform people of the potential risks associated with certain microorganisms by placing them into risk factor groups. Specifically the bacteria *Serratia marcescens* is classified into risk group two. To be considered group two risk factor, the organism must moderately threaten the health of an individual and pose a low threat to public health. The pathogen must further be able to potentially cause serious disease in a human, although this is fairly unlikely to occur. Treatment and preventative measures are available for these pathogens therefore the risk of contraction and spread is low (Human Pathogen and Toxins Act, 2009).

In addition to outlining the general risks of certain pathogens, the HPTA also outlines the conditions in which the general use and disposal of the pathogens must be applied. For pathogens such as *Serratia marcescens* that are categorized in risk group two, use of this organism must be conducted in a research, diagnostic or health services laboratory setting. These are open bench laboratories that often use a biological safety cabinet to dispose of aerosols. Good microbial techniques (GMT) are also practised along with the use of minimal protective clothing to reduce the chance of infection. To safely dispose of level two pathogens, both solid and liquid contaminants must be autoclaved or chemically disinfected (See Table 3). If genetically engineered organisms were created in the experiment, a registration document must be filed describing the nature of these organisms. While working with this species does impart a low risk of potential human infection, there are many accessible treatments to combat any possible infections. Therefore this strain of bacteria is often used as a model organism in specific studies (Human Pathogen

and Toxins Act, 2009).

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Illustrations

Table 1: The following table illustrates the major diseases associated with the *S. marcescens* bacterium. Note that infections involving respiratory and urinary tracts are the most prevalent.

TABLE 1. *Clinical Conditions Accompanying* S. marcescens *Bacteremia.*

CONDITION	NO. OF PATIENTS	PERCENTAGE OF PATIENTS
Pneumonia	23	59
Tracheotomy	13	33
Bronchogenic or laryngeal carcinoma	5	13
Benign prostatic hypertrophy	8	20
Prostatic carcinoma	3	8
Urinary infection	20	51
Coma	13	33
Uremia	8	20
Diabetes mellitus	5	13
Corticosteroid therapy	2	5

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Table 2: The following table illustrates the resistant rates of *S. marcescens* to a variety of antimicrobial agents from 2000 â€“ 2009. The numbers recorded indicate the percentage of the isolates that were found to be resistant.

Antimicrobial agents	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Serratia marcescens										
Total number of isolates	19	33	59	44	187	551	1057	1674	3809	2997
Aztreonam	–	–	–	–	2.3	50.9	52.5	66.9	48.1	53.7
Cefepime	–	–	–	–	–	25.4	30.6	31.9	26.7	48.0
Cefoperazone-sulbactam	0	0	0		0	0	26.1	11.3	21.5	16.7
Cefotaxime	0	0	0	0	0	44.3	45.9	60.0	48.2	49.6
Cefoxitin	–	10.0	50.0	28.6	43.5	61.9	60.2	60.1	67.8	62.9
Ceftazidime	0	0	0	0	0	4.2	15.6	7.9	12.0	26.4
Imipenem	–	0	0	0	0	48.7	54.9	34.2	24.1	18.3
Meropenem	–	–	–	–	–	59.3	40.7	28.2	20.2	10.4
Piperacillin-tazobactam	0	0	0		2.3	27.6	35.2	33.7	30.3	25.1

Adapted from: Zhang R., Ichijo, T., Hu, Y. Y., Zhou, H. W., Yamaguchi, N., Nasu, M., and Chen, G. X. 2012. A ten years (2000–2009) surveillance of resistant Enterobacteriaceae in Zhejiang Province, China. *Microbial ecology in health and disease*. 23: 1-12

Table 3: The following table illustrates the sanitation procedures used in two hospitals for various hospital instruments.

Hospital instruments	n	Cleaning	Solution disinfection	Time (minutes)
Hospital-1				
Bronchoscope	10	e. s. + water	2% glutaraldehyde	15 – 30
EGDs	27	water	2% glutaraldehyde	2 – 5
Colonoscope	30	e. s. + water	2% glutaraldehyde	5 – 15
Hospital-2				
Bronchoscope	10	e. s. + water + us	2% glutaraldehyde	20 – 30
EGDs	42	e. s. + water	2% glutaraldehyde	5 – 10
Colonoscope	30	e. s. + water	2% glutaraldehyde	10 – 20

n = total number of collected samples
e.s. = enzymatic solution
us = ultrasound

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Figure 1: The figure above illustrates colonies of *S. marcescens* streaked onto a nutrient agar. Note the characteristic red appearance of the colonies.

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Figure 2: The figure above illustrates inhibition of prodigiosin pigment of Serratia marcescens by GTN. *, significant P< 0.05

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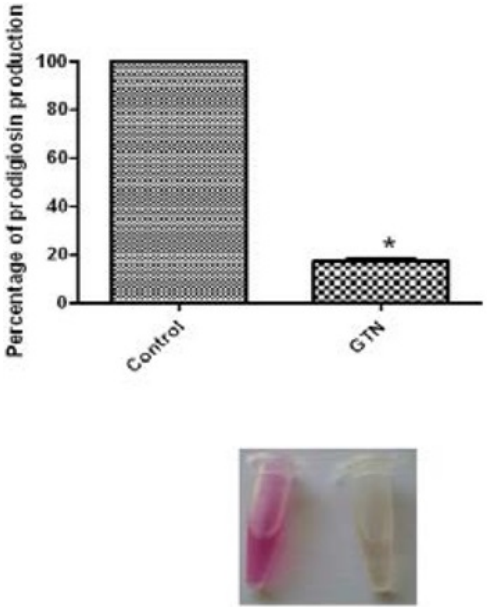

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Figure 3: The figure above shows inhibition of protease production by the skim milk agar method.

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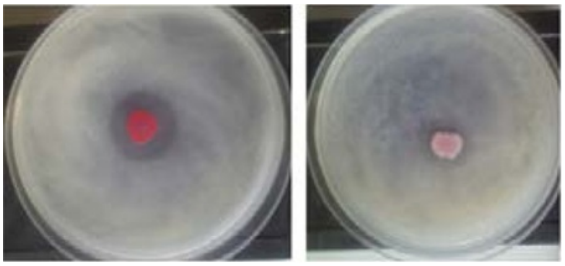

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Figure 4: The figure above demonstrates inhibition of swimming motility by GTN. *, significant P< 0.05.

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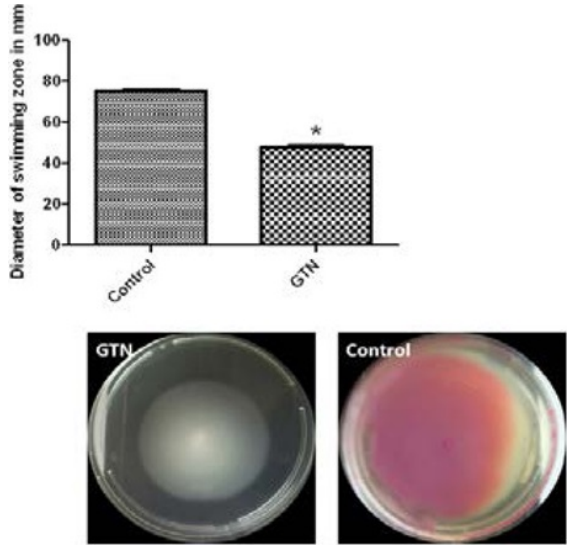

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Figure 5: The figure above shows inhibition of swarming motility by GTN. *, significant P< 0.05.

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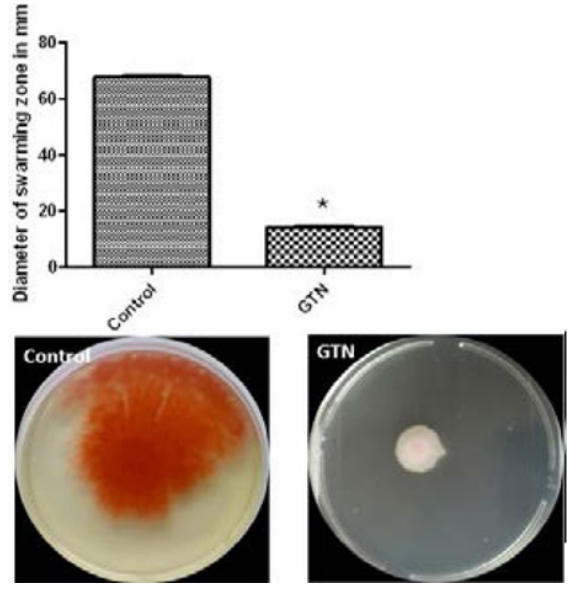

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