

Serratia Infections: from Military Experiments to Current Practice

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INTRODUCTION

Members of the genus *Serratia*, particularly the type species *Serratia marcescens*, cause important infections in humans, animals, and insects. Taxonomically, the genus *Serratia* is confusing, and currently there are 14 recognized species, with 2 subspecies, in the genus (Table 1). This paper describes the colorful history of *S. marcescens* and details clinical infections caused by *S. marcescens* and other members of the genus. First described in 1819, *S. marcescens* was thought to be a nonpathogen for years, although sporadic reports in the medical literature implicated that the organism could cause opportunistic infections. Since many strains of *S. marcescens* have red pigment, and the organism was assumed to be nonpathogenic, it was used as a tracer organism in medical experiments and as a biological warfare test agent. In a now-famous exposé, the U.S. government released *S. marcescens* over both civilian population centers and military training areas from the late 1940s to the mid-1960s in the hopes of gathering data on the potential spread of bioterrorism agents used against the United States. These experiments were unearthed by investigative journalism in the mid-1970s, prompting a congressional investigation that studied U.S. government testing on the public. In the meantime, *S. marcescens* was revealed to be a pathogen capable of causing a full spectrum of clinical disease, from urinary tract infections (UTIs) to pneumonia. *S. marcescens* is now an accepted clinical pathogen, and multiantibiotic-resistant isolates are prevalent. Many of the other members of the genus, though, are rarely isolated in clinical microbiology labs and

hence may not be recognized readily by laboratory personnel. The purpose of this review is to give perspective on the history of *S. marcescens*, provide an update on the taxonomy of the genus *Serratia*, discuss the natural habitats of the bacteria in this genus, update infections that members of the genus *Serratia* cause, particularly in humans, and describe the primary identifying characteristics of these organisms.

HISTORY OF *SERRATIA MARCESCENS*

Early History

In early July 1819, a phenomenon occurred in the province of Padua, Italy, that disturbed many of the peasants in the area, particularly in the town of Legnaro (37, 264). This particular summer had been warmer and more humid than normal, and the polenta, a dish of cornmeal mush made by many families, turned red. Superstitious peasants were fearful of the “bloody polenta,” which was believed to be diabolical in origin. Families refused to stay in homes where the discolored polenta was kept, and one farmer asked for a priest to free his home from “evil spirits” (37, 264). The police were asked to investigate, and they appointed a commission of professors from the University of Padua to assist (37, 264). Bartolomeo Bizio, a pharmacist, studied the phenomenon independently of the University of Padua commission. Bizio conducted experiments wherein he concluded that the red-pigmented polenta was a natural phenomenon in an anonymous paper he authored in August 1819 (37, 49, 264). Bizio successfully cultivated the

TABLE 1. Currently accepted species and subspecies in the genus *Serratia*

Organism	Yr described [reference(s)]	Habitat	Pathogenicity
<i>S. entomophila</i>	1988 (169)	Insects (<i>Costelytra zealandica</i>)	Insects
<i>S. ficaria</i>	1979 (167)	Plants, insects (fig-fig wasp cycle)	Humans
<i>S. fonticola</i>	1979 (145)	Water	Humans
<i>S. glossinae</i>	2010 (146)	Insects (<i>Glossina palpalis gambiensis</i>)	Not reported
<i>S. grimesii</i>	1983 (163)	Water, soil	Not reported (organism has been isolated from human specimens)
<i>S. liquefaciens</i>	1931 (158)	Water, soil, animals, insects, plants	Humans, insects
<i>S. marcescens</i> subsp. <i>marcescens</i>	1823 (37, 264)	Water, soil, animals, insects, plants	Humans, animals, insects
<i>S. marcescens</i> subsp. <i>sakuensis</i>	1998 (109)	Water	Not reported
<i>S. nematodiphila</i>	2009 (425)	Nematodes (<i>Heterorhabditoides chongmingensis</i>)	Not reported
<i>S. odorifera</i>	1978 (165)	Plants	Humans
<i>S. plymuthica</i>	1896 (162)	Water, animals, insects, plants	Humans
<i>S. proteamaculans</i>	1919 (291)	Water, soil, animals, insects, plants	Insects, plants
<i>S. quinivorans</i>	1982 (163)	Water, soil, animals, insects, plants	Humans
<i>S. rubidaea</i>	1940 (363)	Water, plants	Humans
<i>S. ureilytica</i>	2005 (36)	Water	Not reported

organism on fresh polenta in these and subsequent experiments and found that reddish discoloration of the polenta could occur in less than 24 h (37, 49, 264). Bizio did not officially publish his results until 1823, when he wrote a letter to Angelino Bellani, a priest, defending his original anonymous article from a paper written by Pietro Melo, Director of the Botanical Garden at Saonara (49). Melo contended, in a paper he wrote in 1819 after he also investigated the phenomenon, that the discolored polenta was due to spontaneous fermentation that turned the polenta into a “colored mucilage” (49, 144). In his 1823 paper, Bizio determined that the cause of the red polenta was an organism he believed to be a fungus that he named *Serratia marcescens*, after the Italian physicist Serafino Serrati, who pioneered early work on steamboats (37, 49, 264). His description of the genus *Serratia* was “small, stemless fungi; hemispherical capsules occurring in clusters,” and his description of *S. marcescens* was “a very thin vesicle filled at first with a pink, then with a red fluid” (37, 49, 144, 264). Bizio observed that small red spots would appear on the cornmeal mush, get larger, and eventually coalesce into a reddish mass of gelatin. These red spots—colonies—apparently looked like “stemless fungi” (49, 144).

At the same time that Bizio was conducting his independent investigation, Vincenzo Sette accompanied the University of Padua commission. He came to a similar conclusion as Bizio—that the discolored polenta was a result of a natural process. He presented his data on 28 April 1820 but was not able to publish his findings until 1824. Sette named the causative agent *Zaogalactina imetrofa*, and he also thought that the organism looked like a fungus (49).

Then, in 1848, the naturalist Christian Gottfried Ehrenberg investigated red spots that appeared on a cooked potato in Germany. This discoloration was similar to that seen in the red polenta in Italy; however, Ehrenberg was initially unaware of this. He later read Sette’s published results and concluded that this was probably the same phenomenon. Ehrenberg studied the discolored material under a microscope, and with the improved optics of the time, he saw more detail than the researchers in 1819 were able to see. Ehrenberg noticed actual oval cells in the material, believed that the cells were motile, and stated that they divided longitudinally by fission. In addition, he reported seeing flagella. Because of all of these characteristics, he thought the cells were animals and named the agent *Monas prodigiosa* (49, 144).

Over the course of many years, this organism was described by many different names, and taxonomically it is one of the most complicated organisms that has been described. The now accepted name of *S. marcescens* was formally adopted in 1980, when the first “Approved Lists of Bacterial Names” was published (358).

While Ehrenberg is himself part of the history of the discovery of *S. marcescens*, he also looked back at the history of the organism and uncovered a much deeper, ancient past (49, 144). Ehrenberg and other investigators described the propensity of *S. marcescens* to grow on starchy foods, such as bread, and how this growth could be mistaken for fresh blood, especially in times before microorganisms were understood (49, 144). The first reference of “blood” appearing on bread seems to be during the siege of Tyre in 332 B.C. and describes how a seer of the attacking Macedonians said that the “blood” flowing out

of the bread foretold of the fall of Tyre (49, 144, 176). The Macedonians then went on to take the city (144). Many other events of miraculous, “bleeding” bread have apparently occurred throughout history, many of which are associated with the Host of Christianity. References to the “bleeding” of the Host are not entirely ancient; Breed and Breed described an incident that presumably occurred in Naples in 1910 or 1911 of “bleeding Host” in one of the local churches (49). There are many excellent reviews that cover the ancient history of *S. marcescens* and “bleeding bread,” including those written by Breed and Breed (49), Gaughran (144), Harrison (176), and Yu (419).

Use in Medical Experiments

In the late part of the 19th century, William Coley, an oncologist, developed a formula consisting of *Streptococcus pyogenes* and *S. marcescens* that he used to treat sarcoma (219). This treatment, called by names such as Coley’s fluid, Coley’s vaccine, Coley’s toxins, and mixed bacterial vaccine, was first used in patients in 1893 by Coley and continued to be used into the 1960s in the United States (219, 413). This preparation was also used in many other countries, and the German pharmaceutical company Südmedica sold Coley’s toxins under the trade name Vaccineurin until 1990 (219). The efficacy of the treatment has been called into question, but Coley claimed up to 10% cure rates for various types of sarcoma (219).

Meanwhile, the first of several medical experiments with *S. marcescens* as an indicator or tracer organism was conducted by M. H. Gordon in 1906; thus, while the name of the organism was still in question, the pigment characteristics were well known. Gordon was asked to investigate the atmospheric hygiene of the House of Commons in Britain after a recent outbreak of influenza had occurred among the members (9). Gordon, in a now famous experiment, set empty petri plates around him in an empty House of Commons and gargled a liquid culture of *S. marcescens* to determine the spread of the organisms while delivering passages from Shakespeare (10). *S. marcescens* colonies were found on plates far enough away from Gordon to show that microorganisms can be spread from speech in addition to being spread by coughing and sneezing (10). Gordon apparently did not become ill from his experiment (10).

The next tracing experiment occurred just after World War I. On 15 July 1919, Lieutenant Colonel James G. Cumming and Captain J. W. Cox, both Medical Corps officers of the U.S. Army, sprayed the throats, mouths, and lips of five U.S. Army “donor” soldiers with *S. marcescens*. The donors were then instructed to eat and then wash their eating utensils and mess kit in warm water. Following this, five unsprayed “recipient” soldiers washed their utensils and mess kits in the same warm water before eating. Transmission of *S. marcescens* was documented in various percentages from tonsil, tooth, and lip swabs taken from the recipient soldiers, from the mess kits and mess kit wash water, and from the hands of the recipient soldiers. Over the next week, Cumming and Cox conducted two more similar *S. marcescens* transmission experiments with other donor and recipient soldiers (96).

The organism was used as a tracer organism by investigators in medical fields as well. In 1937, Burket and Burn spread *S.*

marcescens on the gums of dental patients from the outpatient clinic at New Haven Hospital, CT, prior to tooth extraction, in an attempt to show that drawing teeth releases bacteria into the circulatory system. Burket and Burn drew blood cultures from the volunteers after painting their gums and isolated *S. marcescens* from 7.5% of the cultures (4/53 cultures) in one set of experiments and from 37.8% of the cultures (14/37 cultures) in another set of experiments. The authors concluded that "the use of *Serratia marcescens* in the present study demonstrated that organisms in the gingival crevice can be forced into the vascular system during extraction" (56). Similar experiments were conducted with *S. marcescens* in 1949 by McEntegart and Porterfield at the University of Liverpool, with 41.4% (12/29 cultures) recovery of *S. marcescens* from blood cultures after the organism was applied to the teeth before extraction (260).

In an attempt to test equipment designed to remove bacteria from air and to show that *S. marcescens* could act as a human pathogen, Captain Tom Paine of the U.S. Army conducted an experiment on 2 October 1945, at Camp Detrick, MD, in which he exposed four individuals to about 2,000,000 viable *S. marcescens* cells per cubic foot of air for 2 1/2 h. Two of the men in the experiment had previously been exposed to *S. marcescens* by accident in another test of equipment designed to remove bacteria from air. Each of the men was admitted to a hospital and monitored. A few hours after the experiments, each of the subjects developed various signs and symptoms, including body aches, malaise, "smarting of the eyes," and green sputum production. Three of the subjects had fever and chills, and two of the subjects still had fever at 24 h postexposure. Four days after the experiment, all of the subjects were asymptomatic (292). Paine does not address whether the men in the experiment were military personnel or civilian volunteers.

Another set of medical experiments using *S. marcescens* was conducted at Harvard in 1957 by Kass and Schneiderman. These investigators applied *S. marcescens*-moistened gauze sponges to different areas of the glans penis of two male patients and to the vulva of a female patient. Each patient had an indwelling catheter, and all were semicomatose. The authors then collected urine from the patients at different times to determine if the presence of the indwelling catheter could facilitate entry of *S. marcescens* into the bladder. Urine that was collected immediately and 24 and 48 h after application of *S. marcescens* was sterile; however, *S. marcescens* was cultured from urine collected at 3 and 4 days postapplication (212).

Next, Waisman and Stone wrote a paper in 1958 describing the "red diaper syndrome," the appearance of *S. marcescens* in soiled diapers of a female baby born in 1954 at the University of Wisconsin. The parents noticed that soiled diapers that had been rinsed with plain water before being placed in a receptacle provided by a commercial diaper laundry service turned red. This first occurred 3 days after the infant had been discharged from the newborn nursery, and after a week, about one-third of the diapers became red after being placed in the receptacle. At this point, the stool of the infant was cultured and *S. marcescens* was recovered. Although the baby never had signs or symptoms of illness, physicians treated her with oral sulfasuxidine. Diapers that followed treatment were less red, but the organism persisted in the baby's intestinal tract for several months. The baby was 2 1/2 years old at the time the paper was written, and no red diapers were observed at that

time. The source of this "red diaper syndrome" was initially a mystery. The other parents who had infants born at the same time and who also stayed in the same newborn nursery were contacted, and red diapers were not observed by any of them. It was learned, however, that a biomedical laboratory that was within 500 yards of the hospital had been using *S. marcescens* in aerosol experiments. Apparently, live organisms were used in the tests and allowed to escape into the air around the laboratory. Another laboratory in an adjoining building reported *S. marcescens* as an airborne contaminant. The *S. marcescens* isolate used by the biomedical lab in the aerosol experiments was compared to the patient's isolate and the contaminant from the other lab, and all three had the same antigenic type (399). Thus, it is more than likely that the baby's *S. marcescens* gastrointestinal colonizer came from the strain used in the aerosol experiments.

Apparently, the use of *S. marcescens* as a tracer organism in dental and medical research was common enough that Thayer wrote a paper in 1966 describing the pathogenic potential of the organism, since human infections had started appearing in the literature for several years under the different names of the organism (377); he felt that using the organism as a tracer in human research was open to debate. In 1970, Whalen wrote a short letter stating that laboratory manuals of the time still described procedures for applying *S. marcescens* to hands and then having students shake hands in an attempt to show how microorganisms can be dispersed (406). By the early 1970s, it was becoming clear that *S. marcescens* could be a pathogen (1, 16, 34, 101, 139, 144, 172, 177, 294, 302, 314, 324, 407), but for years before that, the organism was thought to be a nonpathogen and an ideal tracer organism. In fact, events in the 1970s eventually detailed just how often *S. marcescens* was used as a tracer organism, and not in just medical experiments.

Military Use as a Tracer Organism

In 1977, the U.S. Senate Subcommittee on Health and Scientific Research held hearings that described biological warfare tracer organism tests that the U.S. military had conducted on military bases and the general population from the 1940s through the 1960s (11). One of the organisms used in the tests was *S. marcescens*.

Except for Cumming and Cox studying transmission of *S. marcescens* among soldiers after World War I (96), it is not precisely known when this organism was first used by militaries in tracing experiments. The earliest reference appears in the 1930s, as described by Henry Wickham Steed. Steed, a respected British journalist and previous editor of *The Times*, wrote an article published in 1934 in the periodical *The Nineteenth Century and After* in which he alleged that Germany was actively involved in biological warfare experimentation (191, 322). Steed described documents that he received from sources that contained notes with experiments conducted by the Germans in Paris first on 18 August 1933 (191). According to Steed, German agents released *S. marcescens* aerosols near ventilation shafts at various locations of the Paris Métro, including the Place de la Concorde and probably other sites (191). Other agents had placed plates on various Métro platforms, Steed maintained, such as at the Place de la République, and counted the number of *S. marcescens* colonies in an

attempt to determine the efficiency of aerosol dispersal of a potential biological warfare agent. The documents that Steed obtained also allegedly describe aerial release experiments of *S. marcescens* at the Berlin Tempelhof airfield while the Paris Métro releases were occurring. In addition, other experiments were alleged to have taken place at other locations in France. The documents that Steed received apparently no longer exist, and it is probable that he destroyed them in 1939. The authenticity of the notes, including the obtained microbiological data, has been called into question. For example, data were collected from the Pasteur Station, with the note "95,778 colonies were counted!!! The result was checked an hour later and 91,389 colonies were counted"; thus, the notes seem to indicate that colonies were counted an hour after release in at least one case, and the colony counts are probably too precise as well. Some consider that the documents that Steed received were forgeries. The French took Steed's article very seriously at the time; Germany denied the report (191).

Then, in the mid-1970s, came the news that triggered the U.S. Senate Hearings before the Subcommittee on Health and Scientific Research of the Committee on Human Resources (11). The Long Island newspaper *Newsday* published a report in their 21 November 1976 paper that described tests that the U.S. government had conducted on the population of San Francisco in 1950 and also in the New York City subway system to determine how vulnerable these cities were to a biological warfare weapon attack and also to determine the viability of organisms used in these tests (11, 84). The report said that one person had died of an infection caused by the same organism, *S. marcescens*, used in the tests, and that at least five other patients had been ill with *S. marcescens* infections (11, 85). A month later, on 22 December 1976, the *Washington Post* reported several other instances of tests involving *S. marcescens* and other microbes (*Bacillus globigii* and *Aspergillus fumigatus*) at both military installations and U.S. cities (11). The U.S. Army did acknowledge that testing had been conducted with *S. marcescens* at eight locations on 15 December 1976, so the article in the *Washington Post* probably utilized that information (11). On 23 December 1976, the *Atlanta Constitution* reported eight locations where tests were run, with dates: the Pentagon, Washington, DC (1950); San Francisco (1950); Mechanicsburg, PA (1951); Key West, FL (1952); Fort McClellan, AL (1952); Panama City, FL (1953); Point Mugu-Port Huene, CA (1956); and New York City (1966) (11).

The hearings, which took place on 8 March 1977 and 23 May 1977, revealed that *S. marcescens* had been tested at "public domain" sites, i.e., civilian population areas, a total of at least 7 times, from 18 August 1949, in Washington, DC, until March 1968, in Hawaii. In addition, *S. marcescens* was tested against non-public-domain sites (government and military facilities) at least 29 times, ranging from December 1950, at Naval Amphibious Base, Little Creek, VA, to 16 October 1968, at Edwards Air Force Base, CA (11). Other agents, such as *B. globigii* and *A. fumigatus*, were used in many of the same tests and also in other tests on other sites (11).

In 1981, the grandson of the individual who died from the *S. marcescens* infection in San Francisco in 1950 (11, 407) sued the U.S. government over the testing that allegedly introduced *S. marcescens* to his grandfather (85). The tests in September 1950 were accomplished by U.S. Navy ships releasing aerosols

containing *S. marcescens* and *B. globigii* off the coast of San Francisco; winds then carried the organisms inland (85, 419). Collection stations were established at several inland positions, and *B. globigii* was readily isolated, probably because it is a spore former (85). However, *S. marcescens* was not isolated as readily; it was thought that perhaps the organism had lost its pigmentation and that that was why it was not found by the collection stations (85). In 1951, Wheat and others wrote a paper describing a cluster of probable *S. marcescens* urinary tract infections that occurred in patients at Stanford (407). The authors stated that up until this point, they had not isolated *S. marcescens* at their institution, and that one of the patients had died as a result of an *S. marcescens* infection. About a month before the tests were conducted, the patient who eventually died from the *S. marcescens* infection had developed acute urinary retention while dealing with arteriosclerotic heart disease. A catheter was placed, and a month later his prostate was surgically removed. The patient soon developed a urinary tract infection, and a red-pigmented Gram-negative rod was isolated from his urine. He was eventually admitted, and the same isolate was recovered from blood cultures. The patient died on hospital day 21, of endocarditis. Around the September-October 1950 time frame, four other red-pigmented Gram-negative isolates were recovered from different patient urine cultures, and then six more were recovered from November 1950 to February 1951 (407). The strains isolated at Stanford were not archived and were never compared to the strain used in the testing. Each patient in the Stanford cluster had urinary tract complications, and it is not unusual to see *S. marcescens* nosocomial outbreaks among similar populations (407, 419). Since proof could not be established that the same strain of *S. marcescens* that caused the death of the patient in San Francisco in 1950 was the strain used in the vulnerability tests, the judge did not rule in favor of the patient's family (86).

Farmer and others, in response to concerns in the U.S. press and a paper by Severn that discussed that a potential reason for more reported cases of *S. marcescens* infections in the United States than in other countries was the U.S. government experimentation, conducted a thorough investigation of *S. marcescens* strains that had been collected at the Centers for Disease Control and Prevention (CDC) from 1950 through the publication date of their paper in 1977 (129, 345). The CDC obtained the *S. marcescens* isolate that was used in vulnerability testing from Fort Detrick, where the isolate had been prepared for use in tests, in 1977 and found that it had the same type (*S. marcescens* 8 UK, biotype A6, serotype O8:H3, phage type 678) characteristics as isolates that they had preserved from 1957 and 1969 (129). Thus, the isolate used in the population vulnerability tests was stable (129). Over 2,000 *S. marcescens* cultures were biotyped in the study, and only 20 were of biotype A6, which is a rare biotype (129, 162). There were 7 U.S. isolates that were biotype A6, but only one that was serotype O8:H3; Farmer and others do not relate whether this was a clinical isolate or not, although biotype A6 is usually isolated from the environment (129, 159). In addition, the CDC serotyped over 3,000 *S. marcescens* isolates during the period of this study and found only 7 O8:H3 serotypes; it is not mentioned if any of these were isolated from clinical specimens (129). By 1977, there were more than 100 outbreaks of *S. marcescens* in the United States, and none had the same strain

characteristics as the isolate used in the vulnerability tests (129). Thus, the authors concluded that the strain used in testing was not an important cause of morbidity and mortality in the United States (129).

Several sources make for interesting reading. The *Hearings before the Subcommittee on Health and Scientific Research of the Committee on Human Resources* that describe the congressional investigation are publically available (11). Leonard A. Cole's book *Clouds of Secrecy* discusses the San Francisco *S. marcescens* release, the trial involving the grandson of the individual who died of the *S. marcescens* endocarditis described by Wheat and others, and other events concerning government-sanctioned testing over public areas (84). Yu's 1979 review paper also provides a detailed summary of the military use of *S. marcescens* as a dispersal agent (419).

NOMENCLATURE AND TAXONOMY OF THE GENUS *SERRATIA*

Taxonomy of *S. marcescens*

S. marcescens has one of the most confusing taxonomies in the bacterial world, and part of the confusion no doubt stems from the uncertainty about whether the early descriptions of the organism by Bizio, Sette, Ehrenberg, and others were red- or pink-pigmented yeast or bacteria; microorganisms such as *Rhodotorula* spp., *Methylobacterium* spp., *Roseomonas* spp., *Azospirillum* spp., and others could all potentially have been thought to be the same organism since the 19th century. Also, other red-pigmented *Serratia* species, such as *S. rubidaea* and *S. plymuthica*, could have been confused in some cases with *S. marcescens*, especially since most members of the genus are found in the environment (Fig. 1 shows typical red pigmentation of *S. marcescens* on different types of agar media). In 1920, Winslow and others published the *Final Report of the Committee of the Society of American Bacteriologists on Characterization and Classification of Bacterial Types*, and they named the organism *Erythrobacillus prodigiosus*, following a report by Louis Fortineau in 1904 (411). This was challenged initially in the 1st edition of *Bergey's Manual of Determinative Bacteriology*, in 1923, when Breed wrote that the name *S. marcescens* took precedence over all other proposed names (49). Breed and Breed had performed an extensive study of the history of *S. marcescens* and uncovered Bizio's early work (49). Up until the time that Breed used the name *S. marcescens* in the 1st edition of *Bergey's Manual*, there had been 17 other names used for the organism (144). After *Bergey's Manual of Determinative Bacteriology* was first published, three more names were used for *S. marcescens*: *Salmonella marcescens*, *Salmonella prodigiosum*, and *Chromobacter prodigiosum* (144). *C. prodigiosum*, in particular, was used commonly until the 1950s. Cowan maintained in 1956 that Bizio had studied a yeast and that the resolving power of the microscopes available at the time was not adequate to see a typical Gram-negative bacillus but was probably adequate to see yeast cells (92). Thus, Cowan felt that *S. marcescens* should not be the official name (92). Despite Cowan's objections, the *International Code of Nomenclature of Bacteria and Viruses, Bacteriological Code* (1958) published *S. marcescens* as the official name of the organism (144). Several years later, Gaughran wrote in Bizio's defense that van Leeu-

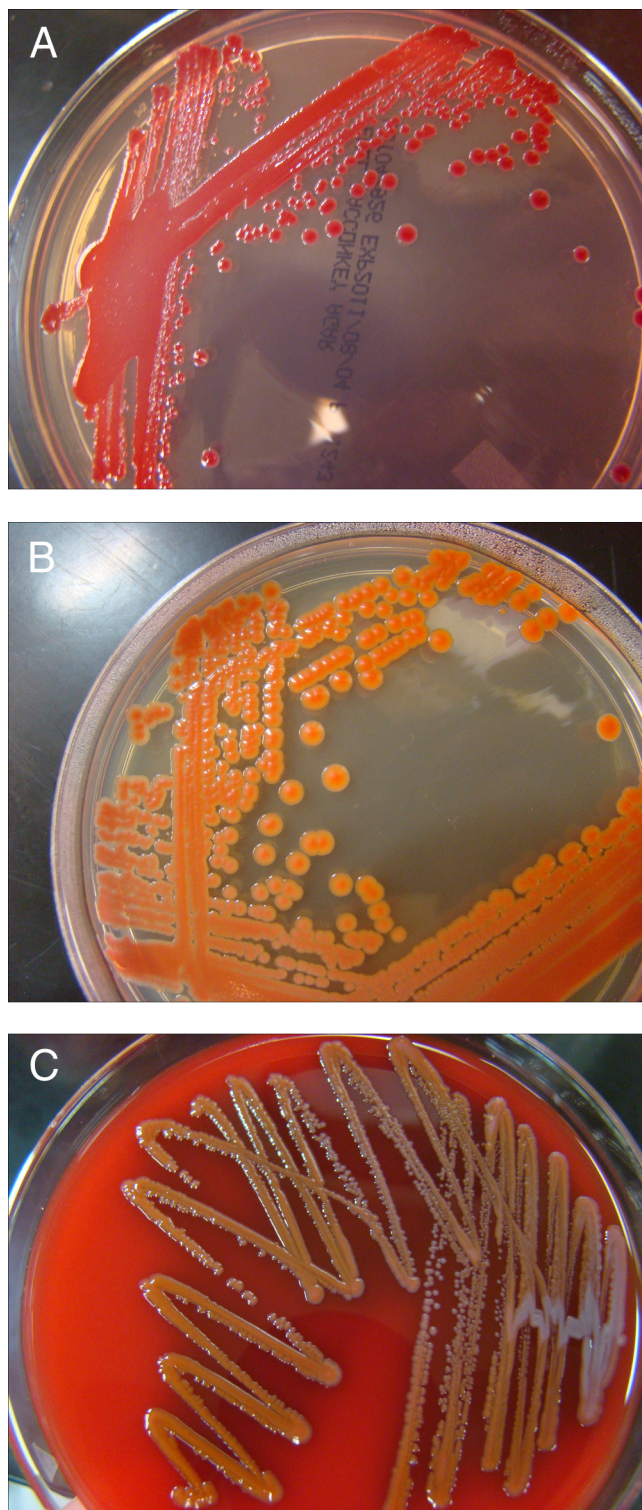


FIG. 1. Red-pigmented colonies of *S. marcescens* on MacConkey agar (A), tryptic soy agar (B), and tryptic soy agar with 5% sheep blood (C). The cultures were incubated at 35°C for 18 h. The MacConkey agar plate was incubated in ambient air, and the other two plates were incubated in 5% CO₂. Each plate was inoculated with the same strain of *S. marcescens*, which was isolated from a case of endophthalmitis.

wenhoek saw individual bacteria in 1683 with his antiquated microscope, so it was certainly possible for Bizio to see a bacterium such as *S. marcescens* in 1819 with the improved optics of the time (144). Gaughran also concluded that Bizio's description of the colonies seems more likely to fit the description for bacterial colonies than yeast cells (144). Every edition of *Bergey's Manual of Determinative Bacteriology* used the name *S. marcescens* throughout the 1900s, and *S. marcescens* was established as the official name in 1980, when "Approved Lists of Bacterial Names" was published under the direction of the International Committee for Systematic Bacteriology (358). Publication of the approved lists of bacterial names also established 1 January 1980 as the new date for determining priorities for names of new taxa, replacing the previously used date of 1 May 1753 (358). In particular, the reviews by Breed and Breed (49) and Gaughran (144) provide comprehensive summaries of the taxonomy of *S. marcescens*.

In 1998, a red-pigmented endospore-forming organism was recovered from a wastewater treatment tank in Saku, Japan (109). At the time, it was reported as a probable *Bacillus* species, but the DNA G+C content resembled that of the genus *Serratia* (2). Numerous studies by Ajithkumar and others were undertaken to determine the identity of the isolate. The DNA G+C content matched that of *S. marcescens* (58 mol%), and the 16S rRNA gene sequence was 99.6% similar to that of *S. marcescens*. Transmission electron microscopy was performed on the isolate, and it had endospores and a Gram-negative type of cell structure. The organism produced prodigiosin, the compound responsible for red pigmentation in many strains of *S. marcescens*, *S. plymuthica*, and *S. rubidaea*, and had the same biochemical pattern as *S. marcescens* (2). The formation of endospores had never before been reported for members of the *Enterobacteriaceae*, and confirmation of the existence of the endospores is now in question; a member of the Subcommittee on the Taxonomy of *Enterobacteriaceae* for the International Committee on Systematics of Prokaryotes has so far not been able to identify spores in the isolate (185). Ajithkumar and others, in the paper where they described this endospore-forming isolate of *S. marcescens*, suggested that the organism may have undergone gene transfer with *Bacillus* species present in the wastewater in order to acquire the ability to form endospores (2). If gene transfer can occur between *S. marcescens* and *Bacillus* species in nature, then perhaps *S. marcescens* may also readily lose the acquired genes. At any rate, the isolate is considered to belong to a subspecies of *S. marcescens*, and at this point it is officially known as *S. marcescens* subsp. *sakuensis*, while the type strain of *S. marcescens* is referred to as *S. marcescens* subsp. *marcescens* (2; <http://www.bacterio.cict.fr/s/serratia.html>).

Taxonomy of Other *Serratia* Species

Confusion exists about the nomenclature of other *Serratia* species as well; see Table 1 for dates that *Serratia* species were described. *S. liquefaciens*, *S. proteamaculans*, *S. quinivorans*, and *S. grimesii* belong to the *S. liquefaciens* complex (159).

S. liquefaciens was first described in 1931 by Grimes and Hennerty, as *Aerobacter liquefaciens* (158). In 1963, this organism was placed in the genus *Enterobacter* (125). Since this

organism was phenotypically similar to *S. marcescens*, *E. liquefaciens* was reassigned as *S. liquefaciens* in 1973 (126).

S. proteamaculans was first identified in 1919, when Paine and Stansfield recovered it from cases of leafspot disease on the tropical flowering plant *Protea cynaroides* (291). At the time, they named it *Pseudomonas proteamaculans*, and the organism has since been renamed several times, including both *Bacterium proteamaculans* and *Phytomonas proteamaculans* in 1930 (166). By 1948, Burkholder had renamed the organism *Xanthomonas proteamaculans* (57), and then Dye classified it as *Erwinia proteamaculans* in 1966 (118). This name held until 1974, when Lelliott wrote that the organism was possibly an *Enterobacter* species but should be excluded from the genus *Erwinia* because of some of its biochemical characteristics (236). Then, in 1978, Grimont and others studied *Erwinia proteamaculans* and concluded that it was synonymous with a strain of *Serratia liquefaciens* (166). The "Approved Lists of Bacterial Names" in 1980 listed both *Serratia proteamaculans* and *S. liquefaciens* as separate species (358), and in 1981 Grimont and others provided evidence that both were indeed distinct (168). In 1982, Grimont and others determined that a biogroup of *S. proteamaculans* should be designated a subspecies, *S. proteamaculans* subsp. *quinovora* (163). Most recently, Ashelford and others proposed in 2002 that this subspecies be elevated to a distinct species, *Serratia quinivorans* (20).

In 1983, Grimont and others described *S. grimesii* after they studied 11 *Serratia* strains that were isolated from water, soil, and human samples; they named the organism after the Irish bacteriologist Michael Grimes, who first described this group (158, 163).

S. rubidaea was originally described by Stapp in 1940 as *Bacterium rubidaeum* and reassigned as a *Serratia* species in 1973 (126, 363). It is a red-pigmented organism, and the species epithet is a contraction of the scientific name for the raspberry plant, *Rubus idaeus*. In 1944, Zobell and Upham described *S. marinorubra*, a red-pigmented organism they isolated from marine water (427). In 1980, the "Approved Lists of Bacterial Names" determined that both species had the same type strain and thus were homotypic synonyms (358). Since they are homotypic synonyms, the name *S. rubidaea* has priority (160).

Apart from *S. marcescens*, the oldest member of the genus *Serratia* is *S. plymuthica*. It was first identified by Fischer in 1887 as a red-pigmented organism isolated from the water supply of Plymouth, England. It was originally called *Bacillus plymouthensis* by Dyar in 1895, but he did not validly publish it, so the first published name of this organism was *Bacterium plymuthicum*, by Lehmann and Neumann in 1896. This organism was then transferred to the genus *Serratia* in 1948 in *Bergey's Manual* and was renamed *S. plymuthica* (162).

The taxonomy of the other currently recognized *Serratia* species is clearer. *S. odorifera* was named in 1978 by Grimont and others, who studied 25 similar strains that were isolated mostly from various human specimens (165). *S. odorifera* is not pigmented and was named for its characteristic potato-like odor (165). Then, Gavini and others found that 20 organisms that had similar characteristics and that were isolated from water were a new species, and they named it *S. fonticola* in 1979 (145). *S. fonticola* does not share many of the key characteristics of other *Serratia* species, such as gelatin hydrolysis

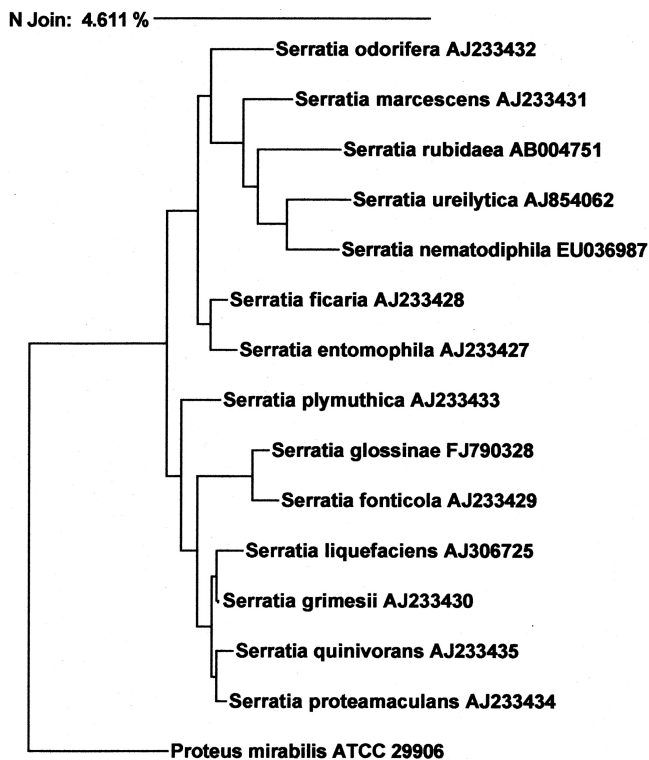


FIG. 2. Dendrogram of the genus *Serratia*, constructed using the neighbor-joining method in MicroSeq software. 16S rRNA gene sequences of type strains of the species, as listed in the List of Prokaryotic Names with Standing in Nomenclature at <http://www.bacterio.cict.fr/s/serratia.html>, were obtained from GenBank. GenBank accession numbers are listed after the species in the dendrogram. The sequence of *Proteus mirabilis*, used as the outgroup, was from the MicroSeq database. The length of the bar at the top represents a 4.611% difference in 16S rRNA gene sequence.

and DNase production, and it has a lower mol% G+C (49 to 52% for *S. fonticola*, compared to 52 to 60% for other members of the genus *Serratia*) (159). Because of this, *S. fonticola* is sometimes thought of as temporarily assigned to the genus *Serratia* (128), but it is still officially listed as a *Serratia* species (159; <http://www.bacterio.cict.fr/s/serratia.html>). By 16S rRNA gene sequence analysis, *S. fonticola* belongs in the genus *Serratia* (Fig. 2) (159).

S. ficaria was also described in 1979, when 14 related strains that were recovered from figs, caprifigs, fig wasps, and a black ant were studied (167). Next, a *Serratia* species that caused amber disease in rot grubs was identified and called *S. entomophila* in 1988 (169). In 2005, *S. ureilytica* was isolated from river water in West Bengal, India (36). In 2009, a red-pigmented organism was isolated from the intestine of *Heterorhabditoides chongmingensis*, an entomopathogenic nematode (425). This isolate, named *S. nematodiphila*, was also fluorescent (425). The most recent accepted species is *S. glossinae*, described in 2010 after it was isolated from the midgut of the tsetse fly (*Glossina palpalis gambiensis*) (146).

Most recently, the species “*S. symbiotica*” was proposed based on DNA and protein phylogenetic studies (54, 230, 330). This bacterium is a secondary symbiont associated with several

different types of aphids and apparently has only recently evolved as a symbiont (55).

Patrick Grimont and Francine Grimont have written many papers describing the members of the genus *Serratia*, including several excellent taxonomy reviews (159–162).

Genomics

To date, only one complete genome has been sequenced for the genus *Serratia*, that of *S. proteamaculans* strain 568 (GenBank accession number CP000826). The genome is 5.45 Mbp, with 4,891 genes encoding proteins, and the strain also has one 46-kb plasmid that was sequenced (GenBank accession number CP000827). The genome was sequenced by the U.S. DOE Joint Genome Institute, and the project can be viewed at [http://www.ncbi.nlm.nih.gov/sites/entrez?Db=genomeprj&Cmd=Search&Term=txid399741\[orgn\]](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=genomeprj&Cmd=Search&Term=txid399741[orgn]).

There are several genomes that are in the process of being sequenced. Two different strains of *S. marcescens*, ATCC 13880 and Db11, are currently being sequenced, by the University of Wisconsin-Genome Evolution Laboratory and the Sanger Institute, respectively. Likewise, two different strains of *S. odorifera*, 4Rx13 and DSM 4582, have been sequenced and are being assembled. The genome of *S. odorifera* strain 4Rx13 is 5.36 Mbp, and that of strain DSM 4582 is 5.13 Mbp.

Two different strains of “*S. symbiotica*” are also being sequenced. “*S. symbiotica*” strain Tucson was sequenced by the University of Arizona and is being assembled. Like those of other symbiotic bacteria, the 2.57-Mbp genome is smaller than that of free-living bacteria. The genome has undergone genetic decay since becoming a symbiote compared to other members of the genus *Serratia* (55). Another strain, *Cinara cedri*, is currently being sequenced by Valencia University.

Lastly, there are several *Serratia* strains that are being sequenced that have not yet been named. These strains have been identified from environmental sources or, in a few cases, from human specimens. A complete listing of complete bacterial genome sequences and genomes that are in the progress of being sequenced can be viewed at <http://www.ncbi.nlm.nih.gov/genomes/lproks.cgi>.

NATURAL DISTRIBUTION OF SERRATIA SPECIES

Since the appearance of the discolored polenta that Bizio and Sette studied, the red-colored potato that Ehrenberg studied, and the earlier findings of “bloody” bread and Host through the ages, it was apparent that *S. marcescens* was readily found in the environment. Because of the confusing taxonomic status of the members of the genus, it was not always readily apparent which natural environments the different species were found in. It is known now, however, that *Serratia* species are commonly found in water and soil and are also associated with plants, insects, and animals. Common habitats of *Serratia* species are listed in Table 1.

Water appears to be a natural environment for several species, including *S. marcescens*, *S. fonticola*, *S. grimesii*, *S. liquefaciens*, *S. plymuthica*, *S. rubidaea*, and *S. ureilytica* (23, 36, 145, 159–162, 209, 416). *S. marcescens*, *S. liquefaciens*, *S. proteamaculans*, *S. grimesii*, and *S. plymuthica* were found in river water in one study, with the predominant species being *S.*

marcescens, followed by *S. liquefaciens* (160). *S. marcescens* subsp. *sakuensis* was originally isolated from the suspended water of a wastewater treatment tank in Japan (2).

Many *Serratia* species are also associated with soil, including *S. marcescens*, *S. grimesii*, *S. liquefaciens*, and *S. quinivorans* (20, 159, 161). Klein isolated what was probably *S. marcescens* from cooked meat and fish in the late 1800s from a wholesale mercantile house in London (220). He theorized that the organism contaminated the food products after soil and graves in an adjoining churchyard had been disturbed; the wind had been blowing toward the mercantile house while the work commenced (220). *S. marcescens* is found naturally in different soil types (23, 142, 161).

Perhaps because *Serratia* species are found in soil, several are associated with plants (161). *S. marcescens* and *S. liquefaciens* appear to be the most commonly plant-linked *Serratia* species and have been isolated from many different types of plants, including grass, tomatoes, green onions, and other vegetables (161). *S. quinivorans* was isolated from soils associated with plants such as sugar beets (20). It is possible that in some cases soil is the source of organisms such as *S. marcescens* isolated from plants. In some cases, though, *Serratia* species are found closely associated with plants and may be important for plant health. For example, *S. plymuthica* is able to stimulate the growth of plants and suppress soilborne plant pathogens (279). Also, *S. liquefaciens*, *S. plymuthica*, and *S. rubidaea* were associated with the rhizosphere of oilseed rape, and all three demonstrated antifungal properties (208). In addition, *S. rubidaea* was found associated with marine alga in one study (209).

S. proteamaculans was originally identified as a cause of leafspot disease of *Protea cynaroides*, the king protea, the national flower of South Africa (291). This organism may be the only *Serratia* species identified that is a phytopathogen, although *S. marcescens* was reported to cause a hypersensitivity reaction when applied to tobacco and bean leaves (229).

One particularly close association of *Serratia* species with plants is that of *S. ficaria* and fig trees. *S. ficaria* has been found in figs in many places in the world, including France, Greece, Sicily, Tunisia, and California (160). *S. ficaria* has also been recovered from fig wasps, which pollinate Smyrna and Calimyrna figs (160). *S. ficaria* was recovered from a patient with endophthalmitis in South Australia; the patient kept figs on his property, so it can be assumed that the organism can be recovered from figs in that part of the world as well (25).

In addition to an association with plants, *Serratia* species are also found in insects, and some species are pathogenic to insects. *S. entomophila* was first found as a cause of amber disease in grass grubs (169), and *S. proteamaculans* has also been found as a cause of amber disease (151, 170). *S. marcescens* is pathogenic to at least 70 species of insects (164). *S. marcescens*, *S. plymuthica*, *S. ficaria*, and *S. liquefaciens* have all been isolated as part of the natural floras of many different kinds of insects, including flies, wasps, termites, and grasshoppers (161). Some of these organisms may also be pathogenic for the same insect varieties (161).

Serratia species are also associated with animals and cause important animal diseases. *S. marcescens* was described in 1958 as a cause of illness in animals, when part of a dairy herd was diagnosed with mastitis (27). There are many other reports of colonization or disease by *Serratia* species in animals, including

but not limited to reptiles, rodents, birds, chicks, goats, pigs, fish, and horses (29, 160). Most recently, *S. marcescens* was identified as the causative agent of white pox disease, a serious threat to the Caribbean elkhorn coral, *Acropora palmata* (301). It is probable that the *S. marcescens* strain responsible for white pox disease in *A. palmata*, which is classified as threatened by the U.S. Endangered Species Act, is of human fecal origin (373). The same *S. marcescens* strain was isolated from two other coral species and from a marine snail from the same region (373).

There are many excellent reviews that cover the natural distribution of *Serratia* species, including those written by Patrick Grimont and Francine Grimont (159–161).

HUMAN INFECTIONS CAUSED BY *SERRATIA* SPECIES

Human infections by members of the genus *Serratia*, particularly *S. marcescens*, were not well recognized until the latter half of the 20th century. This is probably due to the challenge of taxonomically describing the genus and to the fact that several species were not identified until the 1970s and 1980s. *S. marcescens* is now recognized as an important human pathogen; however, many other members of the genus occasionally cause human infections. At this time, *S. entomophila*, *S. glosinae*, *S. proteamaculans*, *S. nematodiphila*, and *S. ureilytica* have not been implicated in human infections.

In large surveys, *Serratia* species account for a relatively low percentage of isolates from different types of infections; while it can be assumed that most of these *Serratia* infections are due to *S. marcescens*, in some cases the species is not established. In a survey of ICU-acquired infections in European countries by the European Centre for Disease Prevention and Control in 2008, *Serratia* species represented 2.0% of all bloodstream infections, ranking organisms from this genus as the 10th most commonly recovered organisms from ICU-acquired bloodstream infections (12). A survey from 1997 data on SENTRY Antimicrobial Surveillance Program isolates from the United States, Canada, and Latin America showed that *Serratia* species were the 12th most common organisms associated with bloodstream infections, accounting for 1.4% of all isolates (107).

For ICU-acquired pneumonia cases from Europe in 2008, *Serratia* species represented 2.8% of all such infections and were the 11th most commonly isolated organisms (12). Data from the SENTRY Antimicrobial Surveillance Program from 2004 to 2008 revealed that *Serratia* species were isolated from 3.5% of all patients hospitalized with pneumonia. In this survey, the incidence of *Serratia* from patients with pneumonia in the United States was 4.1%, while the incidence was 3.2% in Europe and 2.4% in Latin America. Overall, *Serratia* species were the seventh most common cause of pneumonia in hospitalized patients in this study (205).

S. marcescens

S. marcescens is the most commonly isolated *Serratia* species in human infections (160, 233). Like many of the other members of the *Enterobacteriaceae*, *S. marcescens* has been recovered from a large variety of clinical specimens. *S. marcescens* causes central nervous system diseases such as meningitis (16,

314), urinary tract infections (140, 231, 376, 407), pneumonia and other respiratory diseases (1, 34, 172, 413), bloodstream infections, including endocarditis (177, 302, 407), and many different types of wound infections (140, 314).

In 1979, Yu reviewed a few cases of septic arthritis, osteomyelitis, and endocarditis caused by *S. marcescens* in heroin addicts (419), typified by a report by Mills and Drew of 19 endocarditis cases in addicts from San Francisco from 1963 to 1974 (268). At the time, it was thought that *S. marcescens* may be a serious pathogen in drug abusers, but there have not been many reports of *S. marcescens* infections in this patient population since the 1970s, so these types of infections may be sporadic.

At my facility, Madigan Army Medical Center, a U.S. Army health care system that serves active duty military personnel and their dependents, as well as military retirees and their dependents, *S. marcescens* is the ninth most commonly isolated Gram-negative rod and comprised 214 isolates from 156 different patients from 2005 through 2010 (unpublished data). The most frequent source of isolation was respiratory tract specimens (72 isolates; 33.6%), followed by urine specimens (51 isolates; 23.8%) and various wound culture isolates (49 isolates; 22.8%). During the same period, only one other *Serratia* species, *S. liquefaciens*, was isolated from a human specimen at my facility (unpublished data). My hospital is in Pierce County, WA, and in 2009 *S. marcescens* was the eighth most commonly reported Gram-negative rod from Pierce County hospitals (unpublished data).

A large, nationwide survey from Poland from November 2003 to January 2004 revealed that *S. marcescens* was the fifth most commonly recovered organism of the *Enterobacteriaceae* family, representing 4% of all *Enterobacteriaceae* clinical isolates (122). A nationwide survey from Japan from January 2008 to June 2008 showed that *S. marcescens* caused 6.4% of urinary tract infections; *S. marcescens* was the fifth most common cause of urinary tract infections in that study (194).

In the literature, there has been a very large number of reported hospital-related *S. marcescens* outbreaks since the 1950s (>200). Because there are so many described hospital-associated outbreaks, it is often assumed that infections caused by *S. marcescens* are primarily nosocomial in origin. Recently, however, Laupland and others conducted an extensive survey of *Serratia* infections in Canada and found that 65% of all infections caused by *Serratia* species were community based. In this report, *S. marcescens* was the most commonly isolated species, accounting for 92% of all isolated *Serratia* species (233). The literature, however, is dominated by outbreaks and opportunistic infections caused by *S. marcescens*. In addition, *S. marcescens* is an ocular pathogen of note, and not always in hospitalized or immunocompromised patients.

Historical review of infections caused by *S. marcescens* (1900 to 1960). Because of the taxonomic confusion that has existed over the years for members of the genus *Serratia*, and because *S. marcescens* is not always pigmented, reviewing early literature for references of *S. marcescens* infections in humans is somewhat challenging. Most of the papers that describe probable *S. marcescens* infections of humans from the first 60 years of the 20th century attribute the infections to *Chromobacterium prodigiosum*, and in some cases, the authors themselves have questioned the identity of the recovered red-pigmented

organism (172, 302). Part of this confusion can be attributed to early descriptions of the so-called “chromobacteria group.” The chromobacteria were classified as three different bacteria based on their ability to form pigment; thus, “*Chromobacterium prodigiosum*” produced pink or red colonies, *Chromobacterium violaceum* produced a violet pigment, and “*Chromobacterium aquatilis*” produced yellow or orange colonies (407). In addition, biochemical identification of bacteria at the time was not as sophisticated as modern methods, and molecular methods to resolve discrepancies were not available. Thus, the identity of the causative agent in some of the earlier references to *S. marcescens* human infections can be questioned. However, these early cases are informative when viewed together and show a framework of the pathogenic potential of this organism, especially with regard to the ability to cause nosocomial infections or infections in immunocompromised patients. Table 2 summarizes reported, probable *S. marcescens* cases from 1900 to 1960.

The first probable case of reported incidence of human infection by *S. marcescens* was the isolation of a red-pigmented organism, called *Bacterium prodigiosum*, from the sputum of a patient with a chronic cough, published in 1913 by Woodward and Clarke. The patient was not immunocompromised and was apparently healthy prior to infection but had a persistent cough for 3 years. The patient had noticed that his sputum was red and smelled bad, so he consulted a physician because he feared tuberculosis. The investigators noticed that the pigment of the organism was lessened on subculture (413). This case perhaps represented colonization of the respiratory tract by *S. marcescens*, not true infection. Another case of *S. marcescens* isolated from the sputum of a patient with pneumonia was described in the French literature in 1936 (1).

The next published case in the English literature of *S. marcescens* infection in a human was a case of meningitis in a U.S. Army soldier in 1942. The soldier had previously been diagnosed with syphilis, and in July 1941, he had a diagnostic lumbar puncture performed. Antisyphilitic treatment was continued, and the soldier had another lumbar puncture procedure in February 1942. The soldier complained of having cold-like symptoms, including a cough, at this time. In 3 days, the soldier had signs and symptoms of meningitis, and red-pigmented, motile, Gram-negative bacteria that were thought to be *S. marcescens* were isolated from cerebrospinal fluid (CSF) from repeated lumbar punctures. The patient improved and was discharged in May 1942. The source of *S. marcescens* in this case is unclear, but it may have been introduced nosocomially when the patient underwent one of the diagnostic lumbar puncture procedures (16).

Wheat and others described several nosocomial UTIs, with a case of fatal endocarditis, caused by *S. marcescens* in San Francisco in 1951. A year before, the first probable case of *S. marcescens* UTI was described by Gurevitch and Weber, who described a 61-year-old male who was admitted in December 1948 in Jerusalem, Israel, with acute bronchopneumonia. A week after admission, the patient had dysuria, and a red-pigmented organism, identified as “*Serratia*,” was recovered from the urine along with *Escherichia coli* and *Staphylococcus aureus*. Pure cultures of *Serratia* were isolated four more times from the patient's urine over the next 15 days. The authors found that the isolate was similar to *S. marcescens* but had some differences. For exam-

TABLE 2. Summary of *S. marcescens* infections from 1900 to 1960^a

Yr of report	Comments	Reference
1913	Previously healthy patient with chronic cough; red-colored sputum; red-pigmented organism recovered	413
1936	In the French literature; recovered from sputum of patient with pneumonia	1
1942	Meningitis from a U.S. Army soldier who had previously had a diagnostic lumbar puncture performed; red-pigmented organism recovered	16
1948	UTI in patient admitted with acute bronchopneumonia; red-pigmented organism recovered	172
1950–1951	Outbreak of 11 cases of UTI; 1 patient died from endocarditis, presumably from the same isolate; all strains were red pigmented	407
1951	Fatal sepsis in patient who had a gastrectomy because of a duodenal ulcer; red pigmented bacterium recovered	302
1951–1952	Outbreak of 12 cases in a pediatric ward in Israel; several types of infections, including wound infections, skin lesions, meningitis, otitis, and shoulder joint arthritis; 1 fatal case of meningitis in a neonate; outbreak traced to bottle of 5% glucose in saline; all isolates were red pigmented	314
1953	Fatal endocarditis in a patient from the former Gold Coast (Ghana); red-pigmented organism recovered	177
1953	Patient had red-colored sputum after coughing, simulating hemoptysis; red-pigmented organism recovered; similar to 1913 Woodward and Clarke case	139
1957	Empyema in patient with right spontaneous pneumothorax; red-pigmented organism recovered	294
1957	Pseudo-hemoptysis; red-pigmented organism recovered	324
1960	Pneumonia in patient with tubo-ovarian abscess; red-colored sputum; red-pigmented organism recovered	34

^a Infections were assumed to be caused by *S. marcescens* based on the recovery of red-pigmented organisms.

ple, they stated that their isolate grew at 37°C but that *S. marcescens* does not; it is now known that *S. marcescens* will certainly grow at 37°C. Gurevitch and Weber named their isolate “*Serratia urinae*,” but it certainly could have been *S. marcescens* (172). The source of the organism in this case was not clear, but it seems to be nosocomial in origin.

In 1952, a case of *S. marcescens* fatal sepsis was reported by Patterson and others for a 63-year-old male patient with a history of a gastrectomy because of a duodenal ulcer. The previous year, the patient was admitted with hematemesis, melena, and weakness; by hospital day 29, the patient became septic and *S. marcescens* was recovered from several blood cultures. The patient was treated at different times with aureomycin, chloramphenicol, and streptomycin and eventually died

on hospital day 51, despite therapy. The authors stated that the pink-to-red-pigmented isolate resembled the descriptions of both “*Chromobacterium prodigiosum*” and *S. plymuthicum*, but they used the recommended taxonomy of the time to name the organism. Interestingly, Patterson and others reported that UTIs were the most common clinical manifestation of *S. marcescens* in humans. They did not cite a specific reference but cited unpublished data from J. Draper from Bellevue Hospital, NY, who found 2 cases of UTI caused by “chromobacteria” out of 100 UTI cases (302). No data are presented as to the actual identity of the chromobacteria that caused these UTI cases.

Also in 1952, Rabinowitz and Schiffrin reported a fatal case of *S. marcescens* meningitis in a 4-month-old child in Israel. The infant had been admitted originally for enteritis in late 1951 and was initially treated with penicillin and sulfaguandine. Three days later, the infant developed meningitis and *S. marcescens* was recovered from CSF. Therapy had been switched to streptomycin after Gram-negative rods were observed in the CSF, but the infant died. This case occurred among a series of *S. marcescens* infections from the same pediatric ward at the same hospital in Jerusalem. Previously, *S. marcescens* was isolated from wound infections from two other children. After the meningitis case, nine other *S. marcescens* infections occurred in children from the same ward between December 1951 and January 1952; infections in these patients included skin lesions, meningitis, otitis, and shoulder joint arthritis. *S. marcescens* had not been isolated from this hospital previously, and there were no other *S. marcescens* infections on other wards of the same hospital or in other hospitals in Jerusalem. On inspection, it was eventually found that a bottle of 5% glucose in saline that had been administered to children on the ward was contaminated with *S. marcescens*. After the solution was discarded, there were no more *S. marcescens* cases at that hospital (314).

A case of *S. marcescens* endocarditis occurred in 1953 in a 38-year-old patient from the former Gold Coast, now Ghana. The patient was treated with chloramphenicol and streptomycin but eventually died. *S. marcescens* was recovered twice from blood cultures and also from postmortem vegetation material (177).

In 1957, Gale and Lord reported a case of apparent hemoptysis caused by *S. marcescens*. The patient, a 39-year-old veteran, had been coughing up red sputum in 1953, and *S. marcescens* was recovered from the sputum (139). The patient was probably not truly ill with *S. marcescens*. This case is very similar to the case described by Woodward and Clarke in 1913.

S. marcescens was probably the causative agent of a case of empyema in a 55-year-old male patient in Greece with a right spontaneous pneumothorax in 1957. The patient recovered after chloramphenicol treatment (294). In addition, Robinson and Woolley described a case of pseudo-hemoptysis caused by *S. marcescens* in 1957 (324).

In 1960, Bernard and others described a case of *S. marcescens* pneumonia in a 33-year-old female patient who had a tubo-ovarian abscess operated on 5 days before symptoms appeared. Penicillin-sensitive *Staphylococcus aureus* was isolated from abscess material, and the patient was discharged before she developed pneumonia. The patient’s sputum was red, and this was felt by the authors to be due to *S. marcescens* pigmentation. *S. aureus* was also isolated repeatedly from sputum

specimens from the patient. The patient was given penicillin, chloramphenicol, and kanamycin over her hospital stay of 58 days, and she eventually recovered; *S. marcescens* was recovered from 31 sputum cultures over this time (34).

Thus, by the end of the 1950s, several cases of infection in humans due to *S. marcescens* had been described (Table 2). Even so, the belief that *S. marcescens* was a mostly harmless saprophyte persisted. The fact that the organism can be a pathogen under the right circumstances has been seen a great number of times, though, particularly in nosocomial outbreaks and other opportunistic infections.

Opportunistic infections caused by *S. marcescens*. Initial documented cases revealed the pathogenic potential of *S. marcescens*. Several of these infections due to *S. marcescens* were probably hospital acquired in origin, and this bacterium has often been isolated from nosocomial infections or from patients with underlying medical problems. Since *S. marcescens* is often involved in nosocomial infections, one of the dangers associated with the organism is the potential of intrahospital spread and outbreaks. The first paper that described a series of opportunistic infections caused by *S. marcescens* was the report by Wheat and others that described 11 cases of *S. marcescens* UTI, all in adult patients that were immunocompromised to some degree and had indwelling catheters (407). The source of the organism was not clear, and the involved strains were not typed. Wheat and others theorized that risk factors included the indwelling medical devices, the fact that the patients had been ill, and the increased use of antibiotics that may have enabled a normally saprophytic organism to cause disease (407).

The next report of a series of nosocomial infections attributed to *S. marcescens* was the outbreak attributed to contaminated intravenous solutions in a newborn nursery reported by Rabinowitz and Schiffin in 1952. This was the first reported series of nosocomial infections where a reservoir of *S. marcescens* was found (314).

These two case series are fairly typical accounts of *S. marcescens* nosocomial outbreaks or clusters of opportunistic infections. Since the early 1950s, there have been a large number of described outbreaks among both adult and pediatric patient populations.

(i) Opportunistic infections in adult patients. After Wheat et al. described the UTI cases in San Francisco in 1951, the next case series of human infections due to *S. marcescens* was published in 1962 by Gale and Sonnenwirth. During a 6-month period from late 1958 to 1959 at Jewish Hospital, St. Louis, MO, nine patients had infections due to *S. marcescens*. Twelve isolates were recovered from the patients, from wound specimens, empyema drainage, urine, and a throat culture. All of the patients acquired *S. marcescens* during their hospital stay, and all but one of the patients had been treated with antibiotics prior to infection with *S. marcescens*. This information led Gale and Sonnenwirth to theorize, like Wheat and others, that increased antibiotic therapy may enable organisms that are normally not pathogens, such as *S. marcescens*, to cause disease in compromised patients. Eight of the strains were typed at the CDC. The O antigens were type 5 for all strains, while the H antigens of five strains were type 13, that of one strain was type 11, and those of two of the strains were related to both types 11 and 13. Since variability may have been present in H types 11

and 13, all of the strains may have been related (140).

Several cases of UTI occurred at the University of Washington hospital around the same time frame, between 1959 and 1961. Fourteen symptomatic cases of UTI and four probable cases of *S. marcescens* UTI occurred in seriously ill, catheterized patients. *S. marcescens* was recovered from the urine of two other patients without apparent infection. Eight of the isolates were typed at the CDC; only two of the strains had the same type, so this was probably not an outbreak due to a single *S. marcescens* strain (231).

Another series of UTIs caused by *S. marcescens* was described by Taylor and Keane in 1962. A patient with a chronic UTI was transferred to the Manchester Royal Infirmary from another hospital, and *S. marcescens* was isolated from his urine. Within a month, six other patients on the same ward had *S. marcescens* UTIs. Each of the patients were catheterized, leading the authors to suppose that catheterization was a risk factor for *S. marcescens* infection. The *S. marcescens* strains were pigmented at room temperature but not when they were incubated at 37°C (376). Other than biochemical characterization, no strain typing was performed.

During a 1-year period from 1963 to 1964, 181 isolates of *S. marcescens* were recovered from specimens collected from 104 patients at the Yale-New Haven Hospital, New Haven, CT. Of particular interest, only one of the isolates was pigmented. Strains were isolated evenly from clinical specimens throughout the year, and 17 of the isolates were serologically typed at the CDC. Sixteen of the isolates had the same type (O9:H5). All of the patients had an underlying illness, an operation, or both. Most (~80%) of the patients had received antibiotic therapy before infection with *S. marcescens* occurred. Clinical specimens from which *S. marcescens* was isolated included urine, wound specimens, respiratory tract specimens, stool, and blood. The organism was not recovered from environmental sampling in the hospital or from respiratory equipment (81).

Dodson described 16 cases of septicemia due to *S. marcescens* that occurred from 1961 to 1966 at two different hospitals in Birmingham, AL. All of the patients had an underlying disorder, and 13 had received antibiotics prior to septicemia caused by *S. marcescens*. Nine of the patients died, and *S. marcescens* was recovered from specimens other than blood, including sputum and urine, for most patients. The respiratory tract was thought to be a portal of entry for three of the patients, and the genitourinary tract was suspected for four patients who had indwelling bladder catheters. Six of the patients that died had received corticosteroids during therapy, prompting Dodson to conclude that this may have been a risk factor. Several of the *S. marcescens* isolates were not pigmented (108).

Eighty-four pigmented *S. marcescens* isolates were recovered from 49 different patients during a 5-month period from 1967 to 1968 from the same hospital in Columbus, OH. All but one of the patients were adults. *S. marcescens* isolates were recovered from sputum, urine, various wounds, blood cultures, and stool. Rigorous environmental testing was performed in the hospital, and *S. marcescens* was recovered from several intermittent positive-pressure breathing machines, from vials of saline used to prepare injectable medications, and from jugs of saline used to irrigate catheters and wounds. Serologic typ-

ing was performed at the CDC for some of the patient and environmental isolates, and they were found to be of the same type (58).

Since the late 1960s, a tremendous number of nosocomial outbreaks attributed to *S. marcescens* have been described for adult patients; Farmer and others noted that by 1977, more than 100 outbreaks due to *S. marcescens* had been described (129). Outbreaks have occurred in medical wards and medical ICUs (112, 147, 280, 320, 329, 335, 383, 408), a hepatologic intensive care unit (306), various surgery units and wards, including cardiac, urology, and neurosurgery wards (17, 19, 43, 102, 103, 106, 113, 121, 124, 186, 202, 213, 237, 289, 293, 299, 304, 319, 327, 349, 360, 389, 390, 397, 409, 418), dialysis units (223), obstetric wards (365), bone marrow transplant and oncology units (221), a pulmonary ward (391), a gastrointestinal disease ward (382), neurology wards (242, 349), and an outpatient pain clinic (83). In some nosocomial outbreaks, *S. marcescens* was isolated from patients from wards and units throughout hospitals (53, 79, 87, 93, 120, 178, 196, 246, 247, 284, 287, 337, 339, 340, 369, 378, 379). On more extreme occasions, *S. marcescens* strains have been isolated from outbreaks from more than one hospital in a city or area (53, 93, 155, 183, 202, 284, 339, 340). In other incidents, *S. marcescens* nosocomial outbreaks occurred in multiple hospitals in the same city or area, but whether the same strain was involved in all of the hospitals is not clear because typing was not performed (247).

(a) *Multistate outbreaks.* Recently, multistate outbreaks of bloodstream infection due to *S. marcescens* have made headlines. In 2005, two separate outbreaks of *S. marcescens* bloodstream infections were brought to the attention of the CDC, and both were linked to contaminated intravenous magnesium sulfate solutions obtained from a national distributor. The first outbreak occurred in Los Angeles, CA, in January 2005 and involved six patients, all of whom had received intravenous magnesium sulfate and subsequently developed *S. marcescens* bloodstream infections. All six of the *S. marcescens* isolates had identical pulsed-field gel electrophoresis (PFGE) strain typing profiles. The other outbreak occurred in March 2005 in New Jersey and involved five patients. As with the Los Angeles outbreak, all of the patients developed *S. marcescens* bloodstream infections after receiving intravenous magnesium sulfate; again, the isolates had the same PFGE profiles, and the New Jersey and Los Angeles isolates were identical. The same *S. marcescens* isolate was recovered from unopened bags of magnesium sulfate from the same lot. The outbreak officially lasted from 5 January through 26 March 2005, involved 18 total patients, and occurred in three other states besides New Jersey and California (3 cases in North Carolina, 2 cases in New York, and 2 cases in Massachusetts). None of the patients died of *S. marcescens* infection. The magnesium sulfate was produced by a compounding pharmacy; this is significant because compounded pharmaceuticals are held to different regulatory standards than manufactured pharmaceuticals. It is possible that the source of contaminating *S. marcescens* in this case was human hands (372).

Another notable multistate outbreak of bloodstream infection caused by *S. marcescens* was due to contaminated prefilled heparin syringes (38, 354, 370). The outbreak occurred initially from November to December 2007 in Texas, and eventually

nine states were involved, through February 2008 (38, 370). The U.S. Food and Drug Administration inspected the company responsible for preparing the heparin syringes and found that it did not comply with regulatory standards (38). The prefilled heparin was a manufactured pharmaceutical, not a compounded one (38). There were 162 reported bloodstream infections caused by *S. marcescens* due to prefilled heparin syringes from that particular manufacturer, and four of the patients died (38). The outbreak did not stop immediately when the heparin syringe product was recalled (38, 67, 370). This may have been due to contaminated heparin still present in intravenous catheters that was later flushed; however, prefilled saline syringes produced by the same company were also contaminated with *S. marcescens*, and when these were also recalled the outbreak ended (67). Another outbreak of *S. marcescens* bloodstream infections was described for September 2009 in China, where multidose heparin vials were contaminated; this was not due to the same manufactured product that was responsible for the multistate outbreak in the United States (241). In this outbreak, nine patients were affected (241).

(b) *Sources of outbreaks.* Opportunistic infections attributed to *S. marcescens* have been traced to many different sources over the years. Contaminated ultrasonic nebulizers (320), ventilator nebulizers (374), inhalation therapy medications (335), inhalation therapy stock solutions (391), air conditioning units (223, 304), shaving brushes used prior to surgery (237, 408, 409), pressure transducers (30, 112, 397), tap water from pressure-monitoring equipment (327), urine-measuring containers, urinometers, urine-collecting basins, and urinals (147, 329, 349, 356, 418), a cystoscopy area (222), sinks (202, 356), bronchoscopes (304, 353, 389), reusable rectal balloons (61), electrocardiogram leads (360), vitrectomy apparatuses (211), theater linen (124), glass syringes used for preparing intravenous injection fluids (382), saline solutions (66), heparinized saline (375), cream used for obstetric pelvic examinations (365), liquid nonmedicated soap (337), a liquid soap dispenser (374), a finger ring (201), tap water used to take oral medications (186), betamethasone injections (77), an anesthetic (propofol) (33, 181, 278), a narcotic (fentanyl) (289), and transfusion products (315, 342, 403) have all been found to be reservoirs for *S. marcescens*.

Outbreaks associated with either asymptomatic colonized patients or an index, symptomatic colonized patient have occurred several times as well, in some cases including patients colonized in the gut with *S. marcescens* (19, 130, 206, 221, 356). In addition, many outbreaks are attributed to spread by health care workers (106, 112, 178, 196, 201, 280, 289, 299, 304, 339, 340, 390, 409). *S. marcescens* contamination of disinfectant solutions, including chlorhexidine, benzalkonium chloride, and hexetidine, has been affiliated with hospital outbreaks as well (43, 120, 251, 282, 283, 304, 395).

Pseudo-outbreaks due to *S. marcescens* have also been described. In some cases, these have been due to contaminated bronchoscopes, resulting in false-positive culture results from respiratory specimens sent to the laboratory (353, 355). In another case, *S. marcescens*-contaminated EDTA blood-collecting tubes were linked to a pseudo-outbreak of *S. marcescens* bloodstream infections (130).

(c) *Typing methods used in outbreaks.* Various typing methods were utilized to study strains from several outbreaks. In the

1960s and 1970s, serological typing was the primary method used to determine strain relatedness, in addition to phenotypic characteristics and antibiogram similarity. PFGE has been used in many investigations and is a very reliable typing method for *Serratia* outbreaks (26, 77, 83, 113, 181, 183, 201, 211, 246, 289, 304, 349, 369, 374, 382, 391, 395). Enzyme electrophoresis was used to study isolates in at least one study (155). In more recent years, PCR-based typing methods have been used to study the relatedness of *S. marcescens* strains from outbreaks. Repetitive intergenic PCR was used by Liu and others to study an outbreak in a neurology ward (242). Random amplified polymorphic DNA PCR (RAPD-PCR) has also been used (43, 102, 106, 196, 211, 284, 293, 390), as well as amplified fragment length polymorphism (AFLP) analysis (103). One study targeted the flagellin gene of *S. marcescens* for PCR-restriction fragment length polymorphism (PCR-RFLP) analysis (297). The importance of fingerprinting strains has been shown by some circumstances where more than one *S. marcescens* strain was involved in outbreaks or where other *S. marcescens* strains that were not part of an outbreak were isolated from patients in the same hospital (102, 246, 304, 369, 390, 391).

(d) *Outbreak risk factors.* Certain risk factors have shown up time and again in the large number of outbreaks due to *S. marcescens* that have been described for adult patients since the 1950s. Extended hospital stay, prolonged use of antibiotics in inpatients, improper infection control practices by health care workers, immune compromise or underlying medical illnesses, and the use of indwelling medical devices such as catheters are all risk factors. *S. marcescens* strains that have been involved in outbreaks have often been resistant to multiple antibiotics, and this has served to exacerbate infections in hospital settings.

(ii) **Opportunistic infections among pediatric patients.** The outbreak described by Rabinowitz and Schiffrin in 1952 was important in that it was the first outbreak reported for a pediatric population and was also the first outbreak that was traced to a point source, contaminated intravenous solutions (314). In 1966, Stenderup et al. described another case series of *S. marcescens*-related nosocomial infections from Aarhus, Denmark. Thirteen premature infants from the same hospital ward were all infected with the same nonpigmented *S. marcescens* strain from February 1964 to June 1965. Seven of the infants developed septicemia, and six died. The other six infants had purulent conjunctivitis, and all recovered. A source of the organism was not identified (364).

Also in 1966, McCormack and Kunin described another set of infections in newborns in a nursery. *S. marcescens* was recovered from five newborns with UTI and from one newborn each with balanitis, omphalitis, and an upper respiratory tract infection. These infections occurred over a period of 3 months at the University of Virginia Hospital in Charlottesville, VA, and prompted a study of the rate of *S. marcescens* colonization of newborns there. *S. marcescens* was found colonizing the umbilical tract in 64.5% of babies. The likely source was thought to be contaminated saline (259).

Since then, a large number of pediatrics-related outbreaks have been described, and most were reported from the 1980s on. Outbreaks have been noted in neonatal and pediatric ICUs (4, 14, 18, 21, 28, 41, 60, 63, 74, 76, 88, 94, 95, 116, 133, 137, 150,

198, 204, 215, 228, 239, 249, 250, 269, 270, 275, 309, 313, 338, 366, 393, 396, 400, 423), neonatal nurseries/units and special care baby units (7, 100, 156, 190, 238, 275, 310, 359, 362, 387, 423), pediatric oncology units (258), and maternity wards/hospitals (35, 48).

Outbreaks of sepsis/bacteremia (4, 18, 74, 88, 116, 157, 215, 238, 258, 310, 341, 359, 362, 423), meningitis (74, 88, 116, 157, 362, 423), conjunctivitis (74, 88, 116), UTIs (116), respiratory tract infections (74, 88, 116, 285, 359), and wound infections (362) due to *S. marcescens* have all been described for pediatric patients since the series of infections described by McCormack and Kunin in 1966 (259). Conjunctivitis appears to be more common in pediatric population outbreaks in hospitals than in adult populations.

(a) *Sources of outbreaks.* From these pediatric nosocomial infection studies, many environmental sources or point sources have been found as reservoirs for *S. marcescens*, including hands of health care workers and exposure to health care workers (14, 156, 198, 249, 267, 362, 393, 396, 423), contaminated breast milk, formula, and breast pumps (133, 156, 204, 274, 393), contaminated parenteral nutrition (18), an infected neonate as the index patient or colonization of hospitalized infants (28, 63, 100, 148, 238, 269, 270, 275, 338, 362, 400), equipment such as incubators (28, 198), laryngoscopes (95, 204), suction tubes, soap dispensers (52), and waste jars (393), air conditioning ducts (387), contaminated hand brushes (7), contaminated disinfectants and soap (14, 52, 76, 258, 313, 396), cotton wool pads (137), multidose nebulizer dropper bottles (215), and multidose medications (133).

(b) *Typing methods used in outbreaks, as well as risk factors.* As in outbreaks that have occurred in adults, genotyping methods have been used in many pediatric outbreaks to type the involved *S. marcescens* strains, including sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis of disrupted *S. marcescens* cells (116), plasmid profiling (18, 41, 157, 258), PFGE (52, 190, 228, 239, 269, 270, 309, 313, 338, 341, 366, 396), ribotyping (150), rep-PCR (239, 393), RAPD-PCR (18), and PCR fingerprinting (366). Voelz and others performed a systematic analysis of several pediatric *S. marcescens* outbreak studies from 1984 to 2010 that utilized typing procedures to determine clonality. They concluded that either PFGE or PCR-based fingerprinting typing methods were valuable for control of outbreaks. Voelz and others also determined that two or more nosocomially related inpatient *S. marcescens* cases signals a potential outbreak that should be investigated. In addition, they determined that the following precautions should be followed if an *S. marcescens* outbreak is suspected: patients should be isolated, barrier precautions should be utilized, antibiotic therapy should be guided by susceptibility testing and not empirically, and environmental sampling for *S. marcescens* should be performed only if the institution of barrier precautions does not contain the outbreak (398). Voelz and others determined that risk factors for *S. marcescens* outbreaks include exposure to hands of health care workers, length of hospital stay, and use of antibiotics that may eliminate the normal flora of a patient, similar to those often ascertained for outbreaks that have occurred among adults in hospitals (94, 137, 398).

Ocular infections caused by *S. marcescens*. Infections of the eye are an area where *S. marcescens* stands out as a pathogen.

The organism commonly causes hospital-acquired eye infections (particularly in neonates and children) or disease in previously injured eyes of patients; for example, Samonis and others recently reported that ocular infections due to *S. marcescens* were the second most common cause of *Serratia* infections at the University Hospital of Heraklion, Crete, from 2004 to 2009 (333). The organism can, however, also cause eye infections in individuals without eye trauma or an underlying illness. Cases of conjunctivitis, keratoconjunctivitis, endophthalmitis, corneal ulcers, and keratitis due to *S. marcescens* have been described. Since *S. marcescens* is a common environmental organism found in water, soil, and other niches, it is well placed for causing eye infections.

The first reported *S. marcescens* ocular infections of humans occurred among the nosocomial series of infections in premature newborns described by Stenderup et al. in 1966. Six cases of purulent conjunctivitis due to *S. marcescens* were noted. *S. marcescens* was the only organism isolated from eye secretions in four of the infants, while *S. marcescens* was mixed with other organisms in the other two cases. The isolates in these cases were nonpigmented and had the same phenotypic profile, but a common source was not identified (364).

In 1970, Atlee and others described two cases of keratoconjunctivitis caused by *S. marcescens* in Portland, OR. The first patient was a 32-year-old female who was badly burned in a housefire. She developed keratoconjunctivitis a week later, and *S. marcescens* and *S. aureus* were cultured from purulent eye discharge; the *S. marcescens* isolate was nonpigmented. The patient did not have previous eye trauma or infection. *S. marcescens* was recovered from purulent chest, thigh, and cheek lesions over the next 4 weeks, and she eventually died. The second patient was an 82-year-old male with a history of 8 years of bilateral surgical aphakia. After surgery, the patient had gradual bilateral vision loss with scarring and a loss of tear formation. The patient then developed keratoconjunctivitis due to a nonpigmented *S. marcescens* strain. Initial treatment with topical chloramphenicol was unsuccessful, and the patient was given topical neomycin-polymyxin B-dexamethasone. The patient worsened and was given a 4-week course of topical gentamicin, chloramphenicol, and neomycin and systemic ampicillin. *S. marcescens* was cultured during the whole course of treatment. Eye patching, eye expression, and artificial tears were utilized as treatments in addition to antibiotic therapy, and the infection eventually cleared (22).

Lazachek and others described a corneal abscess caused by *S. marcescens* in a 9-year-old girl in 1971 after she was struck in the right eye with a fish hook. The girl was healthy with no underlying medical conditions when the accident occurred, and the source of the organism in this case was probably environmental (234).

Eye infections caused by *S. marcescens* are also associated with the use of contact lenses. *S. marcescens* was the pathogen in 18% to 23% of cases of keratitis in contact lens wearers in two studies (3, 70). In these two studies, *S. marcescens* was tied with *Pseudomonas aeruginosa* as the most common cause of eye infections in contact lens wearers (3, 70). In another study, *S. marcescens* was the most common bacterial isolate from both corneal scrapings and contact lenses obtained from patients with keratitis (99). While *P. aeruginosa* is probably the

most common Gram-negative bacterium associated with ocular infections, *S. marcescens* is also an important eye pathogen, especially among individuals who wear contact lenses.

As shown here, *S. marcescens* has had a long history as a pathogen, and most described cases of human infection due to this organism are nosocomial in origin. While it is the most commonly recovered member of the genus *Serratia* from human clinical specimens, it is not the only *Serratia* species capable of causing illness in humans. Several other *Serratia* species have been identified in human infections, including *S. liquefaciens*, *S. ficaria*, *S. fonticola*, *S. odorifera*, *S. plymuthica*, *S. quinivorans*, and *S. rubidaea*. *S. grimesii* has been recovered from human specimens but has not definitively been found as a human pathogen yet. Table 3 presents a summary of instances when *Serratia* species other than *S. marcescens* were recovered from human clinical specimens.

S. liquefaciens

Although *S. liquefaciens* is isolated infrequently from human clinical samples, it is considered the second most commonly isolated *Serratia* species; in a study by Grimont and Grimont, *S. liquefaciens* was isolated from 2% of 1,108 hospitalized patients in France (160). Determining past infections due to *S. liquefaciens* is complicated, since prior to 1982, this organism was classified as part of the *S. liquefaciens* complex, along with *S. proteamaculans* and *S. grimesii* (163). Because of this, in some cases human infections were reported as caused by the *S. liquefaciens* complex and were not identified to the species level, or infections by *S. proteamaculans* or *S. grimesii* may have been thought to be *S. liquefaciens*. Like *S. marcescens*, *S. liquefaciens* is an environmental organism that has been associated with infections from contaminated medical devices, products, and equipment, including a vitamin C infusion (123), pressure-monitoring equipment (175), neonatal enteral feeding tubes (193), Alsever's solution (252), and endoscopes (261). There have also been several described instances of contaminated blood products with associated transfusion reactions in humans (44, 117, 171, 200, 326, 412).

One of the first documented reports of *S. liquefaciens* isolates from humans was published in 1971, when 21 isolates were recovered from various respiratory, urine, wound, and ulcer clinical specimens. Of these 21 isolates, 6 were thought to be involved in infection, 15 were felt to be commensals, and most were isolated from mixed cultures. Of the six *S. liquefaciens* isolates involved in infection, one was isolated from a fatal case of mucopurulent bronchitis, one was from a case of cellulitis, one was from a gangrenous toe ulcer, and one was isolated from sputum from a case of pneumonia (404).

In 1973, Ewing and others described 24 human isolates of *S. liquefaciens* that had been sent to the CDC between 1957 and 1972 (126). The isolates came from a variety of sites, including blood, several respiratory sources, urine, bile, and feces (126). The authors did not discuss whether any of the isolates were involved in infections. Since that paper was written, several other studies have been published describing the isolation of *S. liquefaciens* from human specimens, and the clinical significance of these isolates is not known (50, 131, 203).

Another early reported case of *S. liquefaciens* infection in a human was described in 1977, when a patient who wore soft

TABLE 3. Summary of infections caused by *Serratia* species other than *S. marcescens*

Organism	Specimen(s)	Comments (references)
<i>S. liquefaciens</i>	Blood, urine, central nervous system specimens, respiratory sites, wounds	Second most common <i>Serratia</i> species involved in human infections (160); also involved in outbreaks (115, 132, 171, 344) and infections with contaminated medical equipment and products (44, 117, 123, 171, 175, 193, 200, 252, 261, 326, 412); like <i>S. marcescens</i> , involved in infections at nearly all sites (6, 15, 50, 75, 90, 115, 123, 126, 131, 132, 171, 174, 203, 262, 266, 271, 276, 308, 326, 332, 336, 344, 361, 401, 404, 412)
<i>S. ficaria</i>	Sputum Leg ulcer Respiratory sites Respiratory secretions Knee wound Gallbladder empyema purulence Blood culture Eye Forearm bite site purulence and blood cultures	Patient with upper respiratory tract infection; patient may have been colonized after eating figs (149) Patient regularly ate figs; organism recovered with 3 other Gram-negative rods (307) Probably a colonizer; no fig association; recovered from two different patients (51) Probably a colonizer (98) Probably a colonizer (98) Four patients infected; gastrointestinal tract was thought to be source for the patients (8, 98) Patient with sepsis; source was probably the gut (98) Patient with endophthalmitis; patient routinely ate figs, but it is unknown if this was source (25) Patient developed cutaneous abscess (97)
<i>S. fonticola</i>	Wound and respiratory tract Leg abscess purulence, blood cultures Right hand wound Stool Scalp wound Synovial fluid	Unknown clinical significance, several isolates (131) After patient had car accident (39) After patient had car accident (305) From an immunocompromised patient with diarrhea (154) Recovered from a hunter after he was bitten by a grizzly bear; recovered with several other bacteria (225) Patient with right knee hemarthrosis after falling off bike into hawthorns (154)
<i>S. grimesii</i>	Several sites Blood cultures Several sites?	Third most common <i>Serratia</i> species recovered from human clinical specimens according to one study by Grimont and Grimont (160) Recovered from three patients, but the clinical significance is not clear (131) Nine strains recovered from human specimens and one from a brain abscess, but the clinical significance is not discussed (368)
<i>S. odorifera</i>	Several sites Primarily respiratory tract specimens Blood cultures, probably other sites Blood cultures, urine Sputum Wound cultures Blood cultures Blood cultures Sputum Urine Blood cultures, urine Sputum, blood cultures	23 strains isolated from human specimens, but clinical significance is not known (165) 22 biogroup 1 isolates, most of which were probably not pathogenic (131) 27 biogroup 2 isolates, most of which were felt to be pathogenic; 1 isolate recovered from a blood culture from a fatal case (131) Patient with cirrhosis and septic shock (71) Acquired nosocomial infection of patient with pulmonary vascular congestion and bilateral pleural effusion (265); biogroup 1 Surveillance cultures from 2 patients in a cardiothoracic surgery unit; both cultures were biogroup 2 (331) Outbreak of sepsis in 8 infants, due to biogroup 1; probably acquired from contaminated parenteral nutrition fluid; all of the infants died (136) Patient with catheter-related sepsis caused by biogroup 1 (152) Patient with bronchial infection due to biogroup 1 (64) Five patients with UTI (263) Fatal sepsis caused by biogroup 1 in a patient with chronic renal failure and diabetes (89) Patient with pneumonia and sepsis caused by biogroup 1 (235)
<i>S. plymuthica</i>	Face wound Respiratory tract Blood cultures, catheter tip Femur wound Blood cultures Wound cultures Peritoneal fluid Blood cultures Blood cultures Peritoneal fluid Right leg wound culture Left femur wound culture	Patient with burn wound, may have acquired organism from a radiator; not thought to be a pathogen (78) Recovered from 5 different patients; no isolates thought to be pathogenic (131) Patient with sepsis (189) Patient with femur fracture who developed wound infection and osteomyelitis (424) Three patients with sepsis (62) Two patients with surgical wounds (62) Patient with abdominal infection (62) Patient with sepsis and community-acquired pneumonia (317) Patient with rectorrhagia and septic shock (111) Patient with peritonitis undergoing peritoneal dialysis (286) Patient with right leg necrotic cellulitis (298) Patient with left femur fracture (277)
<i>S. quinivorans</i>	Bronchial aspirates, a pleural effusion sample, blood cultures	Patient with respiratory distress and pneumonia (40)
<i>S. rubidaea</i>	Several sites Respiratory sites, blood cultures, bile, wound cultures Various sites Left eye Blood cultures Blood cultures, bile Urine Blood cultures	4th most common <i>Serratia</i> species recovered from human specimens according to study by Grimont and Grimont (160) 18 strains sent to CDC; clinical significance is unclear (126) Several strains, but clinical significance not discussed (131, 161, 203) Patient with endophthalmitis after penetrating trauma to left eye (207) Patient with bacteremia (332) Patient with bile tract carcinoma (388) Three cases of UTI (263) Patient with sepsis (343)

contact lenses developed a corneal abscess (90). Contact lens cases were found to be contaminated with *S. liquefaciens* and *S. plymuthica* in one study (266) and with *S. liquefaciens* and *Pseudomonas aeruginosa* in another (336). In the latter study, *S. liquefaciens* and *P. aeruginosa* were also recovered from the contact lenses of the patient, and the patient had developed red eye (336). *S. liquefaciens* has since been found as a cause of eye infections in a few instances (90, 308).

S. liquefaciens has been found as the cause of hospital-acquired outbreaks as well. From 1976 to 1982, six *S. liquefaciens* strains were recovered from infants in a neonatal nursery in East Melbourne, Australia. Three of the infants had life-threatening infections caused by *S. liquefaciens*; the organism was isolated from blood and CSF in one case and from blood in the other two cases. All three of the neonates survived after appropriate treatment (132). In 1984, Serruys-Schoutens and others described a nosocomial outbreak in Belgium involving 10 urinary tract infections due to *S. liquefaciens* that occurred in about a 3-month period. Each of the patients developed a urinary tract infection with the organism after cystometry or cystoscopy. *S. liquefaciens* was isolated from the fluid inside the disposable dome of the cystometer, and the outbreak stopped when the dome was replaced as it should have been. All of the patients recovered uneventfully (344). In addition, Dubouix and others described an outbreak of *S. liquefaciens* among neurosurgery patients in 2005. The organism was isolated from a total of 17 hospitalized patients, primarily from respiratory secretions, but also from urine, a wound, and cerebrospinal fluid. Two of the patients developed sepsis (115).

Probably the most publicized outbreak involving *S. liquefaciens* occurred at a hemodialysis center in Colorado. Ten *S. liquefaciens* bloodstream infections and six pyrogenic reactions (with no bloodstream infection) occurred within a month in 1999 among outpatients at the center, and all but one of the infections occurred in one section of the dialysis center. The dialysis center had pooled single-use vials of epoetin alfa and then administered the drug to the patients. *S. liquefaciens* was recovered from pooled epoetin alfa and from empty vials and, additionally, was found in antibacterial soap and hand lotion. All of the *S. liquefaciens* isolates were identical by PFGE, and the outbreak stopped when pooling of epoetin alfa was discontinued and the soap and lotion were replaced. All of the patients recovered with antimicrobial therapy (171).

There have been several other published case reports involving *S. liquefaciens* as a human pathogen. The organism has been isolated as a cause of abscesses (361), endocarditis (75, 276), a fistulous pyoderma (401), fatal meningoenzephalitis (15), septic arthritis (174), septicemia (6, 115, 123, 132, 171, 326, 332, 412), and urinary tract infections (263, 344) and from a wound culture after a man received a swordfish bill injury (262).

S. ficaria

There have been several instances of *S. ficaria* reported as a causative agent of disease in humans, many of which had a link to figs. The first reported isolation of *S. ficaria* from a human specimen was in 1979, when it was isolated from the sputum of a patient with an upper respiratory tract infection. *S. ficaria* was isolated from the patient's sputum a day or two after she

had eaten a fig, and it was thought that the isolate was probably a transient upper respiratory tract or mouth colonizer (149). *S. ficaria* was isolated from a leg ulcer from a patient in Hawaii in 1980, along with three other Gram-negative rods (307). This isolate was considered to have contributed to disease; it is notable that this patient regularly ate prunes. Pien and Farmer also reported that *S. ficaria* was identified retroactively after being isolated from the nasogastric tube from a patient in Hawaii in 1977, although no other clinical information is available (307). In 1982, *S. ficaria* was cultured from the respiratory specimens of two different patients in Hornu, Belgium. In both cases, *S. ficaria* was felt to be a colonizer. Apparently neither patient had consumed figs, and the source of *S. ficaria* from both patients is not known (51).

In the 1980s and 1990s, *S. ficaria* was isolated several times from human specimens in France. The organism was recovered from respiratory secretions from a patient in 1983 and from a knee wound culture in 1988; in both cases, *S. ficaria* was thought to be a colonizer and a nonpathogen (98). *S. ficaria* was isolated as the cause of infection four different times during the 1990s for purulence from patients with gallbladder empyemas (8, 98). One of the patients had regularly eaten figs, but apparently the timing did not coincide with infection (8). The source of the organism in each of these cases was probably the gut of each patient, so *S. ficaria* may also colonize the human gastrointestinal tract (8, 98). Each of the patients was considered to be immunocompromised prior to infection (8, 98). *S. ficaria* was also recovered from blood from a patient in France with adenocarcinoma of the pyloric antrum who developed septicemia, and this was also thought to be a true infection; again, the patient was immunocompromised (98). The source of *S. ficaria* in this case was also the gut of the patient (98). All of the gallbladder empyema patients and the patient with sepsis responded well to therapy.

In 2002, Badenoch and others reported a case of endophthalmitis caused by *S. ficaria* in a 73-year-old man in Australia. The infection resulted in the loss of the patient's eye. The patient evidently had eaten figs for a large part of his life, but the source of the organism that was recovered from eye cultures is not known. *S. ficaria* could have been a well-established member of the patient's flora by the time the eye infection occurred. The patient had a history of previous eye trauma, so combining this with his age, he was considered to be immunocompromised (25).

The last reported human infection caused by *S. ficaria* occurred in an otherwise healthy 47-year-old man in Greece. The man was a hunter and was bitten by a wild dog on his forearm and his shoulders. A cutaneous abscess developed at the forearm bite site, and *S. ficaria* was isolated from purulence from the abscess and from blood cultures (97). This human infection is probably the first known infection caused by *S. ficaria* in a patient who was not compromised in some way and shows the potential of the organism to be involved in zoonotic infections.

S. fonticola

S. fonticola was first reported from human specimens in 1985, when Farmer and others studied several wound culture and respiratory tract isolates (131). The clinical significance of these isolates is unknown. The first human infection caused by

S. fonticola was reported in 1989, when it was recovered in pure culture from leg abscess purulence and from a blood culture bottle from a 73-year-old female patient who had been in a car accident in France (39). In 1991, *S. fonticola* was isolated as the predominant organism from a right hand infection of a 39-year-old woman after she had also been in a car accident (305). *S. fonticola* was then isolated in 2000 from the stool of an immunosuppressed patient with diarrhea in France (154). *S. fonticola* was later isolated from scalp wounds of a 49-year-old hunter after he was attacked and bitten by a grizzly bear in Alberta, Canada. *S. fonticola* was isolated in this case with several other bacteria, including *S. marcescens* (225). In 2008, *S. fonticola* was recovered from synovial fluid from a 15-year-old boy with right knee hemarthrosis in France. The boy had fallen off a bike and into hawthorns, so it is likely that *S. fonticola* was present on the thorns (154).

S. grimesii

There have been few descriptions of *S. grimesii* isolated from human specimens. Among the 1,108 *Serratia* species from hospitalized patients from France that Grimont and Grimont studied, 0.5% were identified as *S. grimesii*. This ranks *S. grimesii* as the third most commonly isolated *Serratia* species in their study (160). Farmer and others studied three isolates from blood cultures from France, but no clinical information is available for these strains (131). Lastly, nine *S. grimesii* strains from human specimens were described by Stock and others (368). The clinical significance of the strains is not discussed, although one strain was isolated from a brain abscess (368).

S. odorifera

S. odorifera was first named in 1978 when Grimont and others characterized 25 related strains. Twenty-three of the strains were isolated from human specimens, although clinical significance was not established for any of them. Two different biogroups, 1 and 2, have been identified (165). In 1985, Farmer and others described 22 *S. odorifera* biogroup 1 isolates and 30 biogroup 2 isolates; 16 of the biogroup 1 isolates were recovered from human specimens, and 27 of the biogroup 2 isolates were from human specimens. The *S. odorifera* biogroup 1 isolates from this study, most of which were isolated from the respiratory tract, apparently were not actually involved in clinical infections, prompting the authors to doubt the disease potential of biogroup 1 strains. The *S. odorifera* biogroup 2 isolates from this study were more commonly isolated from specimens, though, suggesting a more invasive source, such as blood cultures, although few clinical data were supplied for the strains. One of the blood culture isolates was from a fatal case, but there is no more information available (131).

The first probable case of confirmed human infection caused by *S. odorifera* was reported in 1988 in Florida for a 67-year-old male with cirrhosis. The patient was a chronic alcoholic and was admitted with septic shock. *S. odorifera* biogroup 1 was isolated from both blood and urine. Antibiotic therapy with amikacin and cefotaxime cleared the infection (71). The next documented human case involving *S. odorifera* was a nosocomial infection that occurred in 1990 in Wisconsin in a 73-year-old man admitted with progressive claudication.

The patient had several underlying medical issues, including chronic obstructive pulmonary disorder, chronic renal failure, and severe atherosclerotic vascular disease. The patient developed pulmonary vascular congestion and bilateral pleural effusion while in the hospital, and *S. odorifera* biogroup 1 was cultured from sputum specimens. The patient was treated empirically with tobramycin, metronidazole, ceftriaxone, and trimethoprim-sulfamethoxazole and recovered with ceftriaxone therapy after the identity and susceptibilities of the organisms were determined. The authors also described that two other *S. odorifera* biogroup 1 isolates had been recovered at the University of Wisconsin hospital; both of these isolates were recovered from immunocompromised patients. Both isolates were from sputum, and one was also cultured from a catheter tip (265).

Nosocomial transmission of *S. odorifera* has been documented a few more times since 1990. In 1994, *S. odorifera* biogroup 2 was isolated from surveillance wound cultures from two patients in a cardiothoracic surgery unit at the University of Iowa; the source of *S. odorifera* in these cases is not known (331). Also in 1994, an extreme outbreak due to *S. odorifera* was described by Frean and others, when eight infants died of *S. odorifera* biogroup 1 septicemia because of contaminated infant parenteral nutrition fluid in South Africa. The origin of the contaminated parenteral nutrition fluid was not clear for this outbreak (136).

There have been several other instances of *S. odorifera* infection in humans. In 1994, *S. odorifera* biogroup 1 was reported as a cause of catheter-related sepsis in a 19-year-old woman. The patient had a history of thalassemia major and had a Broviac catheter placed 2 months prior to this infection (152). A bronchial infection due to *S. odorifera* biogroup 1 was reported from France in 1999 (64), and five instances of *S. odorifera* UTI were described from Brazil in 2004 (263). In another case, fatal sepsis caused by *S. odorifera* biogroup 1 occurred in a 73-year-old woman. This patient had a history of cirrhosis, adult-onset insulin-dependent diabetes mellitus, and idiopathic thrombocytopenic purpura and had a left nephrectomy performed 30 years prior. In addition, the patient had chronic renal failure and was receiving long-term dialysis. *S. odorifera* was isolated from several blood cultures and a urine culture in this case (89). Lastly, a case of pneumonia and septicemia caused by *S. odorifera* biogroup 1 was described for a 57-year-old patient with an underlying history of chronic hepatitis C virus infection, alcoholic liver disease, chronic bronchitis, paranoid schizophrenia, and past injection drug use. It is not clear in this case whether the portal of entry in the patient was the lungs or whether the pneumonia was secondary to sepsis (235).

S. plymuthica

Clark and Janda first reported the isolation of *S. plymuthica* from a human clinical specimen in 1985, when the organism was recovered from a surveillance culture from a burn wound on the face of an 8-month-old boy. The boy received the burn wound after falling into a steam radiator, and the organism was probably acquired from the radiator. In this case, *S. plymuthica* was probably not a pathogen (78). In 1985, Farmer and others also described five isolates of *S. plymuthica* that were isolated

from the respiratory tracts of humans; none were from human infections (131).

There have been several reported human infections caused by *S. plymuthica*. The first documented case of *S. plymuthica* infection in humans occurred in 1986 in Westchester County, NY. *S. plymuthica* was isolated from blood cultures and a central venous catheter tip culture from a 54-year-old alcoholic man who had previously been diagnosed with cirrhosis. The patient improved with ampicillin, gentamicin, and clindamycin therapy; the isolate was sensitive to gentamicin (189). A second *S. plymuthica* human infection case occurred in Switzerland in 1987. An 18-year-old patient was admitted with a distal right open femur fracture after a motorcycle accident. The site became infected a few months later, and eventually osteomyelitis developed. *S. plymuthica* was isolated from the wound site as the predominant organism; gentamicin spherules were added to the operation site after wound excision and drainage, and the patient improved (424).

Carrero and others described a series of *S. plymuthica* isolates recovered from blood cultures (three cases) and surgical wound exudate cultures (two cases), with a sixth isolate recovered from peritoneal fluid; the cases all occurred from 1989 to 1990 in Spain and were serious infections. The sepsis and surgical wound culture cases were probably nosocomial in origin, since all of the patients developed infection at least a few days after admission. All of the patients recovered after therapy with drainage, an aminoglycoside, a broad-spectrum cephalosporin, or a combination of an aminoglycoside and a β -lactam antibiotic; however, one patient died due to underlying illness (62).

Another case of *S. plymuthica* sepsis was reported in 1992 for a 50-year-old woman diagnosed with community-acquired bacteremia. The patient presented initially with a 3-day history of dyspnea, a dry cough, and thoracic pain. *S. plymuthica* was recovered from blood cultures, and the patient was successfully treated with a combination of gentamicin and erythromycin (317). A case of nosocomial sepsis caused by *S. plymuthica* in a 79-year-old patient was also described in Spain in 1994. The patient was admitted with rectorrhagia and developed septic shock a week after admission; the patient improved with antimicrobial therapy (111). In 2000, *S. plymuthica* was isolated from a case of peritonitis in a 74-year-old male with continuous ambulatory peritoneal dialysis. The patient was initially treated with gentamicin and vancomycin and did not get better, but he improved after piperacillin was added. The patient, however, died later due to cardiac difficulties (286). *S. plymuthica* was isolated as a cause of necrotic cellulitis from a 66-year-old female patient in 2003. The patient had steroid-dependent asthma and had initially presented with a right inferior extremity contusion wound. She was admitted 2 weeks later with signs of Cushing's disease, and her right leg was red with an erythematous erosion present. *S. plymuthica* was recovered from both blood cultures and from cellulitis cultures. Surgical exploration, debridement, and therapy with imipenem were successful in treating the infection (298). The organism was also involved in a case of septic pseudoarthrosis published in 2008 from a 17-year-old patient with postoperative left thigh pain. The patient had a left femur fracture treated with an osteosynthesis plate 10 months prior to presentation. *S. plymuthica* was recovered from a swab sample taken from pinkish fungos-

ities that were observed around two proximal screws at the site. The patient was treated with ciprofloxacin and gentamicin and recovered (277).

S. quinivorans

The first, and at this time only, human infection caused by *S. quinivorans* occurred in 1990 in France in a 43-year-old homeless man. The patient was an alcoholic and was admitted with a mouth abscess that eventually caused an obstruction, so a tracheotomy tube was placed. The patient later developed respiratory distress and pneumonia. *S. quinivorans* was isolated from bronchial aspirates, a pleural effusion sample, and blood cultures. The patient died of multisystem organ failure a little over a month after admission (40). The patient could have acquired the organism while sleeping outside due to being homeless.

S. rubidaea

While *S. rubidaea* has been isolated from human specimens, its pathogenic potential in humans appears to be very limited. *S. rubidaea* was isolated from 0.2% of 1,108 *Serratia* species from hospitalized patients in France, making it the fourth most common *Serratia* species identified from human specimens in that study (160). *S. rubidaea* has been detected in human specimens from several other studies. In 1973, Ewing and others described 18 *S. rubidaea* strains that were sent to the Centers for Disease Control and Prevention between 1957 and 1972 and had been isolated from the respiratory tract, blood, a few wound specimens, and bile; the authors did not elaborate on whether any of the strains caused infection (126). Since then, *S. rubidaea* has been isolated from human specimens in several studies from various sources (131, 161, 203). The clinical significance of *S. rubidaea* was not described in any of these surveys.

At this time, there have been only a few published cases of human infection by *S. rubidaea*. In 1983, Joondeph and Nothnagel described a case of endophthalmitis caused by *S. rubidaea* in a 10-year-old boy after he had penetrating trauma in his left eye. Treatment with several topical antimicrobial agents cleared the infection (207). A case of *S. rubidaea* bacteremia in a patient with cancer was published in 1989 by Saito and others. The infection was cleared with antibiotic therapy (332). In 1994, *S. rubidaea* was isolated from blood and bile from a 64-year-old female patient with bile tract carcinoma in Spain. The patient recovered after antibiotic treatment. It could not be determined where or how the patient acquired *S. rubidaea*, and it was theorized that the source was endogenous (388). Two other papers since 1996 have described human infections by *S. rubidaea*; three strains were isolated from urinary tract infections in Brazil, and a case of sepsis was described in Tunisia (263, 343).

VIRULENCE FACTORS OF SERRATIA SPECIES

Serratia species are usually opportunistic pathogens, and virulence factors produced by these bacteria are not understood well. All of the species in the genus are motile, and quorum sensing (QS) has been described for some of these organisms.

S. marcescens is capable of producing well-known virulence factors such as fimbriae for adherence (24, 135, 357, 415). In 1997, Hejazi and Falkiner wrote a review paper and summarized the virulence factors known at the time (179).

The *S. marcescens* RssAB-FlhDC-ShlBA Pathway

S. marcescens produces a hemolysin, ShlA, that functions as a pore-forming toxin in concert with another protein, ShlB; together, these proteins cause cytotoxicity in red blood cells and in other eukaryotic cells, such as epithelial cells and fibroblasts (184, 226). They are contact dependent and are not released as extracellular products (184). Without ShlB, ShlA is inactive. ShlB is an outer membrane protein, and it activates and secretes ShlA. Activation of ShlA is also dependent on phosphatidylethanolamine, a primary component of the *S. marcescens* outer membrane. In addition to cytotoxic activity, ShlA also mediates release of inflammatory molecules and apparently contributes to uropathogenicity. Since ShlA and ShlB are cell associated, the ability of these proteins to cause damage usually depends on the ability of *S. marcescens* to adhere to eukaryotic cells (184).

S. marcescens has the ability to swarm at 30°C on Luria-Bertani agar, and swarming has been shown to be a pathogenic factor for *Proteus mirabilis* and *Pseudomonas aeruginosa* (5, 227, 290). At 37°C, a two-component system, RssAB, inhibits swarming and also decreases the production of ShlA (227, 240). Lai and others showed that without the RssAB regulatory system, swarming and hemolytic activities were increased (227). Another system, FlhDC, controls expression of flagella for enteric bacteria and is important for quorum sensing (392). FlhDC also positively regulates production of hemolysin and is involved in swarming and biofilm production in *S. marcescens* (240, 392). When RssAB is activated, *flhDC* expression is reduced, ShlA hemolysin is produced, and biofilm formation occurs (240). If RssAB is deleted or nonfunctional, *flhDC* expression increases, and *S. marcescens* produces increased amounts of hemolysin, swarms, does not form a biofilm, and becomes more virulent (240). The RssAB-FlhDC-ShlBA pathway appears to be important for pathogenesis of *S. marcescens*.

Quorum Sensing in *Serratia* Species

QS, a cell-to-cell signaling mechanism employed by many bacteria, has been described for *S. marcescens*, *S. plymuthica*, and *S. proteamaculans* (243, 392). Quorum sensing is used by bacteria to control certain biological functions, such as biofilm formation and the production of antibiotics (392). When cell populations reach a critical mass, signaling molecules are released that allow bacteria to respond to their environment. Most Gram-negative bacteria, including the aforementioned *Serratia* species, utilize *N*-acyl-homoserine lactones (AHLs) as the signaling molecules in quorum sensing. The QS system is composed of a LuxI-type AHL synthase and a LuxR-type AHL receptor (392).

Various LuxIR-type QS systems have been described for *S. marcescens* strains. In strain MG1 (formerly called *S. liquefaciens*), the SwrI/SwrR system regulates swarming motility, biofilm formation, production of serrawettin, protease, and S-layer protein, and fermentation of butanediol (119). In *S. marcescens* strain 12, the SmaI/SmaR QS system is most re-

lated by sequence to the SwrI/SwrR system from strain MG1 and regulates swarming motility, hemolytic activity, biofilm formation, and production of chitinase and caseinase (91). Another *S. marcescens* strain that has been studied, SS-1, has demonstrated sliding motility that is flagellum independent and regulated by the SpnI/SpnR quorum sensing system (187). Prodigiosin production is also regulated by the SpnI/SpnR system in strain SS-1 (187). The QS system SmaI/SmaR also regulates prodigiosin production and carbapenem biosynthesis in the unnamed *Serratia* sp. strain ATCC 39006 (381).

Different QS systems have also been described for *S. plymuthica* strains. Two separate LuxIR-type systems, SplIR and SpsIR, have been identified in the plant pathogen *S. plymuthica* strain G3 (243). These two QS systems regulate antifungal activity, adhesion, biofilm production, and production of exoenzymes, but not swimming motility, in this strain (243). *S. plymuthica* strain HRO-C48, also a plant pathogen, has a SplIR QS system that also regulates antifungal activity and production of exoenzymes (279). However, the QS system of strain HRO-C48 does not regulate biofilm production or adhesion and does regulate swimming motility (279). Thus, QS systems may be strain dependent and may reflect the particular environment and/or lifestyle of a given strain.

Bacteria that form biofilms are important in medicine because they can colonize catheters and other indwelling devices. In addition, bacteria can form biofilms on contact lenses and contact lens cases, and this has been identified as a risk factor for *P. aeruginosa* eye infections (316). The production of biofilm may represent the typical environmental form of many bacteria and gives several significant advantages, including increased resistance to antibiotics and the immune system (104, 243). Biofilm production has been reported for several *Serratia* species, including *S. marcescens* and *S. plymuthica* (243, 346). Quorum sensing appears to play a role in regulating biofilm production for *Serratia* species, as described above. In addition, Shanks and others found that the oxidative stress response transcription factor OxyR plays a role in *S. marcescens* biofilm formation (346). It is theorized that biofilm production plays an important role in the pathogenesis of *S. marcescens*, although in one study by Pinna and others, isolates of *S. marcescens* and *S. liquefaciens* recovered from soft contact lens-related corneal ulcer cases did not produce biofilms. Rather, it was thought that exoenzymes produced by *S. marcescens* and *S. liquefaciens* may play a role in keratitis (308).

Enzymes Produced by *Serratia* Species

While the ShlAB hemolysin of *S. marcescens* is contact dependent, an extracellular hemolysin was described in 1989 and was recently characterized (153, 351). This hemolysin, PhlA, has phospholipase A activity (351). PhlA does not apparently have direct cytolytic activity; however, it acts upon phospholipid and produces lysophospholipid, which was cytolytic for human, horse, and sheep red blood cells and the HeLa and 5637 cell lines (351).

S. marcescens and other *Serratia* species produce many other enzymes, such as metalloproteases, gelatinase, and alkaline protease, that may enable the organism to cause infections, particularly diseases of the eye (256, 308). Several proteases are described in a review by Matsumoto; the described pro-

TABLE 4. Antibiogram of *S. marcescens* susceptibilities at three different Army medical facilities, in Pierce County, WA, from two MYSTIC surveys, and from the TEST survey

Antibiotic	% Susceptibility ^h (n)						
	Madigan Healthcare System (110) ^a	Pierce County, WA (339) ^b	Tripler Army Medical Center (138) ^c	Walter Reed Army Medical Center (29) ^d	MYSTIC Program European data (195) ^e	TEST U.S. data (427) ^f	MYSTIC Program U.S. data (145) ^g
Amikacin	98	NR	100	100	NR	98.6	NR
Cefepime	100	NR	100	100	NR	96.0	97.9
Ceftazidime	100	100	99	100	93.9	92.3	98.6
Ceftriaxone	97	98	99	97	NR	91.8	95.9
Ciprofloxacin	95	91	94	90	92.3	NR	91.7
Gentamicin	98	99	99	100	96.7	NR	NR
Imipenem	97	98	100	100	99.5	100	97.2
Levofloxacin	100	95	98	97	NR	93.7	95.9
Meropenem	100	NR	NR	NR	100	98.3	97.2
Piperacillin-tazobactam	97	98	97	95	88.7	95.8	93.8
Tobramycin	96	97	91	79	91.5	NR	91.7
Trimethoprim-sulfamethoxazole	100	97	98	NR	NR	NR	NR

^a Combined data for 2008 to 2010. Madigan Healthcare System is located in Tacoma, WA.
^b 2009 data.
^c Combined data for April 2009 to April 2011. Tripler Army Medical Center is located in Honolulu, HI.
^d 2010 data. Walter Reed Army Medical Center is located in Washington, DC.
^e 2007 data on European medical centers from the MYSTIC Program (386). Data are for the following *Serratia* species: *S. marcescens* (170 isolates), *S. liquefaciens* (19 isolates), unidentified *Serratia* species (3 isolates), *S. fonticola* (2 isolates), and *S. odorifera* (1 isolate).
^f 2007 data on U.S. medical centers from the Tigecycline Evaluation and Surveillance Trial (TEST) (114).
^g 2008 data on U.S. medical centers from the MYSTIC Program (318). Data are for the following *Serratia* species: *S. marcescens* (119 isolates), *S. liquefaciens* (5 isolates), and unidentified *Serratia* species (21 isolates).
^h NR, not reported.

teases affect defense-related humoral proteins and various types of tissue cells (256). A recently described metalloprotease from *S. grimesii*, grimelysin, is proteolytic for actin (46). *E. coli* that expressed grimelysin was able to invade Hep-2 cells, so this metalloprotease may allow bacterial internalization into eukaryotic cells (47).

ANTIMICROBIAL RESISTANCE OF SERRATIA SPECIES

As with most literature regarding *Serratia* species, the vast majority of antimicrobial resistance that has been described for this genus has occurred in *S. marcescens*. The fact that *S. marcescens* was a very resistant organism was recognized in early published cases. For example, Wheat and others, in their seminal report of 11 cases of UTI from San Francisco in 1951, reported probable resistance of the isolate that caused fatal endocarditis to polymyxin B, terramycin (oxytetracycline), chloramphenicol, streptomycin, and penicillin, with moderate sensitivity to sulfonamides (407). It is now known that *S. marcescens* is frequently resistant to multiple antibiotics. Outbreaks caused by multiply resistant *S. marcescens* strains have been described, and many *S. marcescens* strains carry both chromosomally encoded and plasmid-mediated resistance determinants for several different types of antibiotics. Indeed, one of the hallmarks of nosocomial outbreaks due to *S. marcescens* is very resistant strains, making such outbreaks even more devastating for compromised patients.

Typical Resistance Patterns of *Serratia* Isolates

Like other members of the *Enterobacteriaceae*, *S. marcescens* and other *Serratia* species are intrinsically resistant to penicillin G, the macrolides, clindamycin, linezolid, the glycopeptides,

quinupristin-dalfopristin, and rifampin (244, 367, 368). In addition, most members of the genus *Serratia*, including *S. marcescens*, are usually resistant to ampicillin, amoxicillin, amoxicillin-clavulanate, ampicillin-sulbactam, narrow-spectrum cephalosporins, cephamycins, cefuroxime, nitrofurantoin, and colistin (82, 244, 367, 368). If a *Serratia* isolate tests susceptible to one of these antibiotics, the result should be viewed with suspicion and retested. *S. marcescens*, *S. odorifera*, and *S. rubidaea* were intrinsically resistant to tetracycline in studies by Stock and others (367, 368). *S. marcescens* also harbors a chromosomal *ampC* gene that can extend resistance to several more β -lactam antibiotics. In addition, some strains carry chromosomally encoded carbapenemases, and plasmid-mediated enzymes can be acquired that further extend resistance to β -lactams. Sensitivities to other antimicrobials, such as the quinolones and trimethoprim-sulfamethoxazole, are more variable. In general, most *Serratia* species are sensitive to the aminoglycosides (367, 368). Sensitivity of *S. marcescens* strains to aminoglycosides, though, is more variable, and *S. marcescens* has a chromosomal aminoglycoside resistance gene that may contribute to decreased susceptibility. At my medical facility in Tacoma, WA, most *S. marcescens* isolates are sensitive to commonly prescribed antimicrobial agents. Antibiogram data for 110 different patient isolates recovered from clinically significant infections are shown in Table 4, compared to data for Pierce County, WA, and two other U.S. Army medical facilities (Tripler Army Medical Center, Honolulu, HI, and Walter Reed Army Medical Center, Washington, DC), 2007 data from European medical centers from the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program (386), 2007 U.S. data from the Tigecycline Evaluation and Surveillance Trial (TEST) (114), and 2008 U.S. data from

the MYSTIC Program (318). The MYSTIC Program antibiograms represent primarily *S. marcescens* data but also include other *Serratia* species. The 2007 MYSTIC Program data presented in Table 4 summarize antimicrobial sensitivities for 195 *Serratia* isolates (*S. marcescens*, 170 isolates; *S. liquefaciens*, 19 isolates; unidentified *Serratia* spp., 3 isolates; *S. fonticola*, 2 isolates; and *S. odorifera*, 1 isolate) collected from 28 different European hospitals (386). The 2008 MYSTIC Program data were collected from 15 different U.S. medical centers and show data for 145 *Serratia* isolates (*S. marcescens*, 119 isolates; *S. liquefaciens*, 5 isolates; and unidentified *Serratia* spp., 21 isolates) (318).

Aminoglycoside Resistance in *Serratia*

Aminoglycoside-modifying enzymes are the most common mechanism of aminoglycoside resistance in bacteria. These enzymes modify their targets, aminoglycosides, by adding either an acetyl group (*N*-acetyltransferases [AAC]), a phosphate group (*O*-phosphotransferases [APH]), or a nucleotide (*O*-nucleotidyltransferases [ANT]). The antibiotic then does not bind to the ribosome target. The aminoglycoside-modifying enzymes are usually acquired by bacteria via genes on plasmids. Aminoglycoside resistance in bacteria can also occur because of alteration of the ribosome target, cell impermeability, or efflux. Another type of enzyme, a 16S rRNA methylase called RmtB, has been identified in *S. marcescens* (110). This enzyme is plasmid mediated and provides high-level resistance to several aminoglycosides, including kanamycin, tobramycin, amikacin, gentamicin, streptomycin, and arbekacin (110). Other plasmid-mediated 16S rRNA methylases have been identified in *S. marcescens*, including ArmA, RmtA, and RmtC (210).

S. marcescens harbors a chromosomal aminoglycoside-modifying enzyme of the AAC(6') family, AAC(6')-Ic (65). Enzymes of the AAC(6')-I class are 6'-*N*-acetyltransferases and are clinically significant in that they may provide resistance to several commonly prescribed aminoglycosides, such as amikacin, tobramycin, and netilmicin. The *S. marcescens* chromosomally encoded AAC(6')-Ic enzyme is normally expressed weakly or at low levels, and because of this, *S. marcescens* is normally sensitive to aminoglycosides, and susceptibilities of these antibiotics can be reported. Treatment with amikacin, tobramycin, or netilmicin, though, may result in selection of a hyperproducing mutant of the chromosomal enzyme. In this case, an AAC(6')-Ic-hyperproducing strain will be resistant to amikacin, tobramycin, netilmicin, neomycin, and kanamycin (244, 347).

In a survey published in 1985, 19.2% of aminoglycoside-resistant Gram-negative rods in the United States were *Serratia* isolates (350). Of these isolates, 69% carried 6'-*N*-acetyltransferases. Another 18.4% of these *Serratia* strains carried the ANT(2'') enzyme, a 2''-*O*-nucleotidyltransferase; this enzyme confers resistance to gentamicin, tobramycin, and other aminoglycosides. Perhaps more ominously, 47.8% of *Serratia* strains carried both a 6'-*N*-acetyltransferase and the ANT(2'') enzyme, and this combination of determinants confers resistance to nearly all of the clinically useful aminoglycosides. The same survey also found that 42.7% of the examined aminoglycoside-resistant Gram-negative rods from Japan, Korea, and Formosa were *Serratia* isolates. Nearly all of these strains (97.9%) car-

ried a 6'-*N*-acetyltransferase, and 71.4% harbored both a 6'-*N*-acetyltransferase and the ANT(2'') enzyme (350).

In another study, antimicrobial sensitivities of a large number of Gram-negative rod isolates that were recovered from ICU patients from hospitals throughout the United States from 1993 to 2004 were examined. *S. marcescens* was the sixth most commonly isolated organism, representing 5.5% of all Gram-negative rods from the study. Antimicrobial sensitivity data were shown for 2002 to 2004, and 7.1% of the *S. marcescens* strains were resistant to tobramycin, with 0.8% resistant to amikacin; an additional 5.8% and 1.1% of *S. marcescens* strains had intermediate resistance to tobramycin and amikacin, respectively (245).

Another recent study evaluated amikacin resistance in *Enterobacteriaceae* isolates from 1995 to 1998 and 2001 to 2006 from a university hospital in South Korea. In this study, 7.5% of *S. marcescens* isolates were resistant to amikacin, and most of the resistant strains were isolated from 2001 to 2006. Six of the *S. marcescens* strains carried both ArmA and AAC(6')-1b on plasmids. In this study, there were only four other *Serratia* species recovered from clinical specimens, and none were resistant to amikacin (210).

Many nosocomial outbreaks in both pediatric and adult patients have occurred with *S. marcescens* strains resistant to one or more aminoglycosides (17, 41, 53, 79, 88, 93, 120, 238, 258, 280, 285, 287, 339, 356, 423). Most of the initial reports of aminoglycoside-resistant *S. marcescens* nosocomial outbreaks occurred in the mid- to late 1970s (for example, see references 79, 93, and 339). The outbreak described by Craven and others in 1977 is a useful study of probable selection of a hyperproducing aminoglycoside-resistant mutant. Two adjacent hospitals associated with the University of Texas Health Science Center experienced a 22-month nosocomial outbreak of gentamicin-resistant *S. marcescens* infections. Amikacin was given to 19 patients during this time. Four severely ill patients died within 2 days of being given amikacin; the authors felt that *S. marcescens* was a key factor in the death of each patient. Ten other patients who were not as ill had *S. marcescens* infections that responded well to amikacin therapy. *S. marcescens* infections persisted in the other five patients. In four of these persistent infections, the isolates were initially sensitive to amikacin but became resistant over time. Two of these patients died, one after 7 days of amikacin therapy, and the other after 18 days of amikacin therapy (93).

β -Lactam Resistance in *Serratia* Species

As already discussed, *Serratia* species are intrinsically resistant to several β -lactam antibiotics, including penicillin G, ampicillin, amoxicillin, amoxicillin-clavulanate, cefuroxime, and narrow-spectrum cephalosporins. All *Serratia* species are intrinsically sensitive to carbapenems, although some *S. marcescens* strains have been identified that harbor chromosomal carbapenemases. In addition, most of the members of the genus *Serratia* carry a chromosomal *ampC* gene, and there have been several descriptions of strains acquiring plasmid-mediated extended-spectrum β -lactamases (ESBLs).

Chromosomal AmpC β -lactamases of *Serratia* species. AmpC β -lactamases are classified as either group 1 enzymes by the Bush scheme or class C enzymes by the Ambler

scheme (197). They hydrolyze primarily cephalosporins, including the cephamycins, although these enzymes have activity against the penicillins and aztreonam (197). The chromosomal *ampC* genes of *S. marcescens* and several other members of the *Enterobacteriaceae* are inducible by various β -lactam antibiotics by a complex mechanism that involves cell wall recycling (173). The 5'-untranslated region (5'-UTR) of the *S. marcescens* chromosomal *ampC* gene was found to be 126 bases long (248). This is longer than those for other *Enterobacteriaceae* organisms with chromosomal *ampC* genes. Sequence analysis of the *S. marcescens ampC* 5'-UTR predicted a stem-loop structure that provides stability to *S. marcescens ampC* mRNA (248).

Typically, the expression of AmpC is low from *S. marcescens* and other members of the *Enterobacteriaceae* (173, 197). Induction of the chromosomal *ampC* gene causes an increase in AmpC β -lactamase production and increases the MICs of several β -lactams (173, 197). Strong inducers of *ampC* in enteric bacteria such as *S. marcescens* include cefoxitin, imipenem, ampicillin, amoxicillin, benzylpenicillin, and narrow-spectrum cephalosporins, including cephalothin and cefazolin (197). Broad-spectrum cephalosporins, such as ceftazidime, cefotaxime, and ceftriaxone, and other β -lactams, including cefepime, cefuroxime, and aztreonam, are weak inducers (197). Overexpression of AmpC β -lactamase in *S. marcescens* and other *Enterobacteriaceae*, however, is most often due to a mutation or deletion in the induction/cell wall recycling pathway (173, 197). These mutants, called derepressed mutants, are clinically important and may result in treatment failures with β -lactam antibiotics (197, 244). While *S. marcescens* and other *Serratia* species are not intrinsically resistant to broad-spectrum cephalosporins, the use of these antimicrobials in treating *Serratia* infections is hazardous because the emergence of derepressed *ampC* mutants occurs more often with these agents than with other antimicrobials (197, 244). The 2011 Clinical and Laboratory Standards Institute (CLSI) *Performance Standards for Antimicrobial Susceptibility Testing (M100-S21)* (82) includes this warning concerning treatment with broad-spectrum (third-generation) cephalosporins: "*Enterobacter*, *Citrobacter*, and *Serratia* may develop resistance during prolonged therapy with third-generation cephalosporins. Therefore, isolates that are initially susceptible may become resistant within 3 to 4 days after initiation of therapy. Testing of repeat isolates may be warranted." Some medical facilities may use this as a statement if they choose to report broad-spectrum cephalosporin susceptibilities for *Serratia* species. At my medical facility, we do not report broad-spectrum cephalosporin susceptibility test results for *Serratia* species, although *S. marcescens* isolates from 2008 to 2010 were 100% sensitive to ceftazidime and 97% sensitive to ceftriaxone (Table 4).

An outbreak of a multiply antibiotic-resistant *S. marcescens* clone occurred in Italy from 2001 to 2002 and may have been due to *ampC* derepression or induction. The outbreak occurred among 13 patients, and 12 of the patients had been treated with various β -lactams before isolation of *S. marcescens*. The *S. marcescens* clone in this cluster was resistant to penicillins, aztreonam, and expanded- and broad-spectrum cephalosporins and was sensitive to carbapenems and cefepime (26).

An outbreak due to *S. marcescens* expressing an AmpC-like

β -lactamase, S4, was described in Taiwan from 1999 to 2003. A total of 58 strains carried this S4 β -lactamase, and all were recovered from patients with bloodstream infections. Strains expressing S4 were resistant to cefotaxime but not ceftazidime (420).

Data on chromosomal *ampC* genes of other *Serratia* species are more limited. In one study, β -lactam sensitivity patterns indicated that isolates of *S. liquefaciens*, *S. grimesii*, and *S. proteamaculans* harbored chromosomal *ampC* genes (368). The sequence of the *S. proteamaculans* strain 568 genome indicates the presence of a chromosomal *ampC* genes and several other β -lactamases. In another study, *S. ficaria*, *S. fonticola*, *S. odorifera*, *S. plymuthica*, and *S. rubidaea* were shown to have chromosomal *ampC* genes (367). The *ampC* genes of *S. ficaria*, *S. fonticola*, and *S. odorifera* were inducible in this study, while the *ampC* genes of *S. rubidaea* and four of five strains of *S. plymuthica* were not (367). In a study from India of isolates recovered from different types of clinical specimens from 2007 to 2008, 25.6% of *Serratia* isolates produced AmpCs, 40% of which were inducible, and 60% of these isolates were derepressed mutants. Besides *S. marcescens*, the authors did not identify the isolates to the species level (321).

There are several excellent AmpC-related reviews, including those written by Jacoby (197) and Hanson and Sanders (173).

Carbapenem resistance in *Serratia* species. Carbapenems such as imipenem and meropenem are important antibiotics, since they are often used to treat severe infections caused by *Enterobacteriaceae* organisms resistant to broad-spectrum cephalosporins. Carbapenem resistance is uncommon in *Serratia* species (367, 368). A carbapenemase, eventually called SME-1, was first found in two *S. marcescens* isolates in 1982 in England (417). These isolates were both resistant to imipenem and had reduced sensitivity to meropenem (417). In addition, the two isolates were fully sensitive to broad-spectrum cephalosporins (417). Since then, two other SME-type enzymes have been described: SME-2 and SME-3 (311). The SME-type carbapenemases are class A enzymes that have a serine at the active site (311). These enzymes are not ubiquitous in *S. marcescens* strains, and at this point, only sporadic infections with *S. marcescens* isolates expressing SME carbapenemases in the United States have been described (105, 312). The SME-type carbapenemases strongly hydrolyze penicillins, narrow-spectrum cephalosporins, carbapenems, and aztreonam, weakly hydrolyze broad-spectrum cephalosporins, and are inhibited by clavulanate (311).

Another chromosomal class A carbapenemase, designated SFC-1, was found in an environmental strain of *S. fonticola* from Portugal (180). This strain was also found to harbor a metallo- β -lactamase called Sfh-I (180). This strain was resistant to both meropenem and imipenem (180). However, neither of the enzymes has been found in other strains of *S. fonticola* (180, 402).

Plasmid-mediated carbapenemases have also been found in *S. marcescens*. From 2006 to 2007, an outbreak of 21 plasmid-mediated, KPC-2-expressing *S. marcescens* strains was reported from China. All of the isolates were of the same clone and either were resistant to carbapenems or exhibited reduced susceptibility to carbapenems (59). KPC class carbapenemases were first discovered in *K. pneumoniae* in 1996, and these class A β -lactamases strongly hydrolyze all of the β -lactams and are

plasmid mediated (311). A smaller outbreak of KPC-2-expressing *S. marcescens* was reported from Greece in 2008 to 2009, when three strains were recovered that had reduced susceptibility to carbapenems (385). In 2009, an *S. marcescens* isolate that was resistant to imipenem, meropenem, ertapenem, and doripenem was recovered from the sputum of a patient with pneumonia. The *S. marcescens* isolate probably acquired the carbapenemase by plasmid transfer from an *E. coli* isolate that the patient was also infected with; the *E. coli* isolate had probably previously acquired the carbapenemase from a *Klebsiella pneumoniae* isolate, again from the same patient. The carbapenemase from each of the bacteria was a KPC-3 enzyme (352). KPC enzymes have been found in *S. marcescens* on other occasions; a KPC-2 enzyme was identified from an isolate from China in 2006, and a KPC-3 enzyme was identified from an isolate from New York City in 2000 (105, 426). The appearance of different KPC enzymes in *S. marcescens* isolates from several different geographic locations is alarming, especially since these carbapenemases mediate such high-level resistance to carbapenems and other β -lactams.

Another plasmid-mediated carbapenemase, GES-1, was found in all strains from 15 patients in another outbreak caused by *S. marcescens* in a Dutch hospital from 2002 to 2003 (106). The GES carbapenemases are also class A enzymes that are plasmid mediated (402). GES-1 exhibits low-level carbapenemase activity and was initially classified as an ESBL because it hydrolyzed penicillin and broad-spectrum cephalosporins (311, 402).

Plasmid-mediated class B metallo- β -lactamases have also been identified in *S. marcescens*. The metallo- β -lactamases hydrolyze carbapenems, are not inhibited by β -lactamase inhibitors, are inhibited by metal ion chelators, and have zinc ions at the active site (311). There are several plasmid-borne metallo- β -lactamase genes, and the first found in *S. marcescens* encoded an IMP-1 enzyme (288). This enzyme, produced from an *S. marcescens* strain with high-level resistance to several β -lactam antibiotics, including imipenem and meropenem, was recovered from a patient in 1991 in Japan (288). Since then, various plasmid-mediated IMP enzymes have been found in *S. marcescens* several times, including from a few outbreaks (182, 303). Another type of plasmid-encoded metallo- β -lactamase, VIM, has been found in *S. marcescens* (422) and *S. liquefaciens* (271). A survey of *Serratia* species from clinical isolates from India in 2007 to 2008 found that 15.4% produced metallo- β -lactamases, although the type of enzyme was not determined, and besides *S. marcescens*, the other *Serratia* species were not identified (321).

Lastly, an outbreak of meropenem-resistant *S. marcescens* in 2005 occurred in South Korea among nine different patients. None of the isolates carried a carbapenemase, and resistance to carbapenems was probably due to overproduction of the chromosomally encoded AmpC enzyme and to loss of outer membrane protein F (OmpF) (371).

Excellent reviews about carbapenemases include those written by Queenan and Bush (311) and Walther-Rasmussen and Høiby (402).

ESBLs in *Serratia* species. The broad-spectrum cephalosporins were introduced in the early 1980s and were used to treat infections by organisms with β -lactamases such as TEM and SHV (300). The ESBLs are plasmid-mediated enzymes that have activity against the narrow-, expanded-,

and broad-spectrum cephalosporins, the penicillins, and aztreonam (300). There are a wide variety of ESBLs, including TEM-, SHV-, OXA-, and CTX-M-type enzymes. There are several reports of ESBL-expressing *S. marcescens* isolates. In some cases, ESBL-expressing *S. marcescens* strains have caused outbreaks (94, 196, 281, 284, 293). *S. marcescens* strains most commonly carry CTX-M-type ESBLs (69, 196, 218, 273, 284, 293, 295, 414, 421) but have also been found carrying SHV (218, 281, 284, 295), TEM (218, 284, 295), and a novel ESBL, BES-1 (42).

The prevalence of ESBLs in *S. marcescens* varies. In Taiwan, 12.2% of *S. marcescens* strains recovered from clinical specimens over about a 6-month period from 2001 to 2002 produced ESBLs. All of the ESBLs from this study were identified as CTX-M-3, and 33% of the patients with ESBL-producing *S. marcescens* died (69). In another study of *S. marcescens* isolates recovered from several hospitals in 2005 in Taiwan, 16% showed phenotypic ESBL production (resistance to ceftazidime, ceftriaxone, or cefepime); molecular characterization of ESBLs was not conducted (199). Rates of ESBL-producing *S. marcescens* from South Korea range from 12.4% (72) to 30.6% (214). In a study from Thailand, 24.1% of *S. marcescens* isolates recovered from 2006 to 2007 were ESBL producers; the isolates carried mixtures of CTX-M-, SHV-, and TEM-type enzymes (218). A survey of *S. marcescens* isolates from 2006 to 2009 in Mexico revealed that 20.5% were ESBL producers, and all of the ESBLs were SHV-type enzymes (143). In India, Rizvi and others found that 33% of *Serratia* species recovered from various clinical specimens from 2007 to 2008 were ESBL producers; they did not determine the type of enzymes present and did not report which species of *Serratia* were present besides *S. marcescens* (321).

Several studies have been conducted in Poland to examine ESBL-producing *Serratia* species. In a survey from two hospitals in Danzig from 1996 to 2000, 19% of *S. marcescens* isolates produced ESBLs (284). Most (84%) expressed CTX-M-type enzymes (284). In one alarming national report for 2003 to 2004, enteric bacteria from 13 different hospitals in Poland were studied for ESBL production. In this study, 70.8% of *S. marcescens* strains were ESBL producers (122). Most (80.1%) carried CTX-M-type enzymes, while the rest produced SHV-type ESBLs. Another Polish study also showed alarming results. In this survey, 77.8% of *S. marcescens* isolates from 2005 from a transplantation unit exhibited phenotypic ESBL production; molecular characterization of isolates was not performed. The authors found, though, that 26.3% of *S. marcescens* isolates recovered from patients from other wards of the same hospital expressed phenotypic ESBL production (272).

An excellent ESBL review is that written by Paterson and Bonomo (300).

Quinolone Resistance in *Serratia* Species

Quinolones target DNA gyrase and topoisomerase IV (325). DNA gyrase, encoded by *gyrA* and *gyrB*, is a type II topoisomerase that is essential for DNA replication and transcription (325). In general, *Serratia* species are often fairly sensitive to quinolones (367, 368). At my institution, 95% of *S. marcescens* strains recovered from 2008 to 2010 were sensitive to cipro-

floxacin, and during this time, all (100%) strains were sensitive to levofloxacin (Table 4). Sheng and others, however, found that fluoroquinolone sensitivity decreased in *S. marcescens* and other Gram-negative bacteria from the mid-1980s to the late 1990s in Taiwan (348). For example, 99% of *S. marcescens* isolates recovered from 1985 to 1986 were sensitive to ciprofloxacin, but only 80% of isolates from 1996 to 1997 were sensitive to ciprofloxacin (348). In the two studies of *Serratia* susceptibilities performed by Stock and others, all of the *Serratia* species tested were sensitive to the quinolones, although reduced sensitivities were observed with some strains of *S. marcescens* and *S. rubidaea* (367, 368).

When quinolone resistance in *Serratia* species does occur, it can be by a variety of mechanisms, as with other Gram-negative rods, and has most often been described for *S. marcescens*. *S. marcescens* has chromosomal determinants for quinolone resistance and also may develop resistance by acquiring plasmids or by mutation.

Alterations in *gyrA* have commonly been shown to be involved in quinolone resistance (405). In 1991, a spontaneous ciprofloxacin-resistant mutant of an intrinsically ciprofloxacin-sensitive *S. marcescens* isolate was recovered after incubation on medium containing 0.5 µg/ml of ciprofloxacin (254). This spontaneous resistance was due to a *gyrA* mutation (254). *gyrA* mutations in several quinolone-resistant *Enterobacteriaceae* strains, including *S. marcescens*, were studied by Weigel and others (405). This group found that there were several single amino acid substitutions in GyrA that enabled fluoroquinolone resistance in *S. marcescens* (405). Kim and others also studied quinolone-resistant *S. marcescens* strains and found two different single amino acid substitutions in GyrA (216).

Alteration of outer membrane proteins was reported as a cause of quinolone resistance (and also resistance to aminoglycosides and some β-lactams) in *S. marcescens* in the mid-1980s (334). Omp1 appears to be the primary porin that allows ciprofloxacin entry into *S. marcescens*, and Omp1-deficient strains had higher MICs than those for the parent strains for several antibiotics, including ciprofloxacin and β-lactams such as cefoxitin, ceftriaxone, cefotaxime, and moxalactam (328).

Efflux pumps are a common cause of quinolone resistance, especially in Gram-negative bacteria (31). At this point, three different chromosomally mediated efflux pumps of the resistance-nodulation-cell division (RND) family have been identified in *S. marcescens*: SdeAB, SdeCDE, and SdeXY. The SdeCDE pump appears to be selective and provides resistance to novobiocin (31). Norfloxacin and tetracycline are substrates for SdeXY, so this pump also appears to be fairly selective (68). The primary efflux pump of *S. marcescens* that utilizes quinolones as substrates appears to be SdeAB, and it provides resistance to ciprofloxacin, norfloxacin, and ofloxacin (31, 224). SdeAB also acts as an active efflux pump for chloramphenicol, sodium dodecyl sulfate, ethidium bromide, and *n*-hexane (224). Interestingly, it was shown that exposure of *S. marcescens* to cetylpyridinium chloride, a quaternary ammonium disinfectant, caused mutations in SdeAB that increased resistance to norfloxacin, biocides, and several other antibiotics (255). Another efflux pump characterized from *S. marcescens*, SmdAB, belongs to the ATP-binding cassette (ABC) family (257). When cloned into *E. coli*, this pump provided elevated MICs for several antimicrobials, including the quinolones cipro-

rofloxacin, norfloxacin, ofloxacin, and nalidixic acid (257). Efflux pumps have not been well characterized for other *Serratia* species, but several are predicted from the genome sequence of *S. proteamaculans* strain 568.

Another mechanism of quinolone resistance in bacteria is via the plasmid-mediated *qnr* genes. The *qnr* genes, *qnrA*, *qnrB*, *qnrS*, *qnrC*, and *qnrD*, code for pentapeptide repeat proteins that block quinolones from acting upon their targets. The effect of these Qnr proteins is usually low-level resistance to quinolones (253). While Qnr-mediated quinolone resistance is not often high, the presence of these determinants appears to enable further selection of more resistant mutants (253). In a 2007 study from Korea, *qnr* genes were found in 2.4% (4/166 strains) of *S. marcescens* strains; one isolate had a *qnrA1* gene, two had *qnrB1* genes, and one had a *qnrB4* gene (296).

A chromosomally mediated type of *qnr* gene was found in an *S. marcescens* isolate from Spain by Velasco and others. This *qnr* gene, called Smaqnr, has 80% homology to *qnrB1* and was responsible for decreased ciprofloxacin susceptibility. The authors identified chromosomally carried Smaqnr in 14 other *S. marcescens* clinical isolates, so it may be widely distributed (394). Chromosomal *qnr* genes have been found in many other Gram-negative and Gram-positive bacteria (325).

Recently, *aac(6′)-Ib-cr*, a variant of the aminoglycoside-modifying determinant *aac(6′)-Ib*, was found to modify ciprofloxacin by acetylation and to cause low-level resistance. The *aac(6′)-Ib-cr* gene is plasmid mediated and was shown to be additive with *qnrA* in determining ciprofloxacin resistance (323). To date, this plasmid-mediated gene has been found in two *S. marcescens* clinical isolates from South Korea. Both strains also had a plasmid-mediated *qnr* gene; one had *qnrA1*, and the other had *qnrB1*. The isolate with the *qnrA1* gene had higher MICs for both ciprofloxacin (4 µg/ml) and nalidixic acid (32 µg/ml) than the isolate with the *qnrB1* gene (0.125 µg/ml for ciprofloxacin and 2 µg/ml for nalidixic acid) (217).

Rodríguez-Martínez and others provide a recent, detailed review on quinolone resistance (325).

Resistance to the Tetracyclines in *Serratia* Species

In general, many *Serratia* species exhibit intrinsic resistance to the tetracyclines (367, 368). All *S. marcescens* and *S. liquefaciens* isolates were resistant to tetracycline in the 2003 study by Stock and others, and most strains were resistant to other tetracyclines, such as doxycycline and minocycline (368). Thus, tetracycline, doxycycline, and minocycline are generally not good choices of therapy for *S. marcescens*. Resistance to the tetracyclines in *Serratia* has so far been described as mediated by either chromosomally mediated or plasmid-mediated efflux pumps.

Some of the described chromosomally mediated efflux pumps that mediate quinolone resistance may also be responsible for tetracycline resistance. Tetracycline is a substrate for the RND pump SdeXY (68). Matsuo and others showed that the ABC pump SmdAB provided increased tetracycline resistance when it was cloned into a susceptible *E. coli* strain (257). In addition, the RND pump SdeAB was shown to provide an increase in tetracycline resistance after *S. marcescens* was exposed to cetylpyridinium chloride (255). Also, a tetracycline-specific efflux pump, encoded by *tetA*(41), was identified in an

S. marcescens strain recovered from a heavy metal-contaminated stream. The *tetA*(41) gene was not found on a plasmid, so it is probably located on the *S. marcescens* chromosome (380).

Plasmid-mediated tetracycline resistance determinants have been identified in *S. marcescens* as well. The *tetA*, *tetB*, *tetC*, and *tetE* genes have all been found in *S. marcescens* strains. These genes all code for efflux pumps. Tetracycline and minocycline are substrates for TetB, but the other pumps primarily transport tetracycline (73).

Tigecycline, a glycylcycline, was approved for human use in the United States in the mid-2000s. Tigecycline has shown promise against Gram-negative bacteria because it is more stable in the presence of tetracycline-specific efflux pumps such as TetA and TetB than other tetracyclines. Fritsche and others determined tigecycline susceptibilities of tetracycline-resistant *Enterobacteriaceae* organisms recovered from around the world from 2000 to 2004. Most of the enteric isolates were sensitive to tigecycline; however, a small percentage of *S. marcescens* isolates (2.4%) were resistant (138). In 2004, the Tigecycline Evaluation and Surveillance Trial (TEST) was initiated as a global survey to evaluate the effectiveness of tigecycline against Gram-negative and Gram-positive bacteria. In the United States, 96.6% of *S. marcescens* isolates ($n = 678$) in 2005 were sensitive to tigecycline; in 2006, 96.8% ($n = 593$) were sensitive, and in 2007, 95.8% ($n = 427$) were sensitive (114). The resistance of some strains of *S. marcescens* to tigecycline is probably due to intrinsic efflux; Hornsey and others demonstrated that upregulation of the RND efflux pump SdeXY mediates tigecycline, ciprofloxacin, and cefpirome resistance (188). More clinical data need to be collected regarding the use of tigecycline for treatment of *Serratia* infections.

Trimethoprim-Sulfamethoxazole Resistance in *Serratia* Species

Trimethoprim and sulfamethoxazole were first used in combination in 1968, and together they act synergistically to inhibit folic acid synthesis in bacteria. Sulfamethoxazole inhibits dihydropteroate synthetase (DHPS), an enzyme that catalyzes the formation of dihydrofolate from *para*-aminobenzoic acid. Trimethoprim acts on the next step of the pathway, by inhibiting the enzyme dihydrofolate reductase (DHFR); this enzyme catalyzes the conversion of dihydrofolate into tetrahydrofolate (192). *Serratia* species are generally thought to be susceptible to trimethoprim-sulfamethoxazole (367, 368). At my institution, all 110 *S. marcescens* strains recovered from clinical samples from 2008 to 2010 were sensitive to trimethoprim-sulfamethoxazole (Table 4).

There are several potential mechanisms of resistance to trimethoprim and sulfamethoxazole, including cell impermeability and/or efflux pumps, intrinsically insensitive DHPS or DHFR, acquired insensitive DHPS or DHFR, and mutations, recombination events, or regulatory changes that occur in DHPS or DHFR. At least 20 transferable *dhfr* genes that mediate trimethoprim resistance have been described; *dhfr*_I and different types of *dhfr*_{II} are most common, especially among the *Enterobacteriaceae*. At this point, two transferable genes, *sul*_I and *sul*_{II}, have been found that mediate resistance to sulfonamides (192).

While *Serratia* species are usually considered to be sensitive to trimethoprim-sulfamethoxazole, this may depend on the geographic area the organisms are recovered from; high resistance rates have been described over the years in several studies. In a study from Beirut, Lebanon, from 1994, Araj and others reported that 56% of *Serratia* species recovered from a variety of clinical sites were resistant to trimethoprim-sulfamethoxazole, compared to 12 to 48% resistance in Saudi Arabia, 50% resistance in Kuwait, and no resistance in the United States (13). From 1997 to 1999, *S. marcescens* isolates recovered from respiratory sites were 64 to 75% sensitive to trimethoprim-sulfamethoxazole in Italy (134). National antimicrobial resistance surveillance in Taiwan from the year 2000 indicated that 62% of *S. marcescens* isolates were resistant to trimethoprim-sulfamethoxazole (232). In a recent survey from Nicaragua, 27.3% of *S. marcescens* isolates recovered in 2008 were resistant to trimethoprim-sulfamethoxazole (45). In contrast, most (98.1%) *Serratia* species recovered in Canada from 2000 to 2005 were sensitive to trimethoprim-sulfamethoxazole (233).

Few studies have determined the actual mechanism of resistance to trimethoprim-sulfamethoxazole in *Serratia* species. One study of trimethoprim-resistant *Enterobacteriaceae* from Greece found two *S. marcescens* isolates with plasmid-mediated *dhfr*_{II} genes, and nine total *S. marcescens* isolates that were resistant to trimethoprim were recovered from urine specimens (384). Huovinen described trimethoprim resistance due to impaired permeability with *S. marcescens* (192). Given the facts that several efflux pumps have been identified in *S. marcescens* and that several more appear likely to be identified from the genome sequence of strain DB11, it is possible that trimethoprim and/or sulfonamide resistance may also be mediated by an efflux mechanism.

Treatment of *Serratia* Species Infections

Because *Serratia* species are intrinsically resistant to a large number of antibiotics, there are fewer treatment options for these organisms than for many other bacteria. Multiresistant *Serratia* strains are routinely isolated from human clinical infections, and highly resistant strains have been causative agents in many outbreaks, but a glance at Table 4 reveals that the majority of strains from different locations in the United States and Europe are sensitive to commonly reported antibiotics. Health care providers may empirically treat suspected *Serratia* infections with piperacillin-tazobactam, a fluoroquinolone, an aminoglycoside, and/or a carbapenem and then modify treatment based on actual susceptibility test results when available. At my institution, therapy with piperacillin-tazobactam, an aminoglycoside, and/or a carbapenem is usually successful in treating serious *Serratia* infections.

LABORATORY IDENTIFICATION OF *SERRATIA* SPECIES

The members of the genus *Serratia* are in the family *Enterobacteriaceae* and are not particularly difficult to cultivate from clinical specimens. Identification of *Serratia* species, though, can be difficult, and since species besides *S. marcescens* are capable of causing human infections, it is important to reliably

identify these organisms to the species level, especially since strains of *Serratia* species are often multiply antibiotic resistant. As members of the *Enterobacteriaceae*, all *Serratia* species are Gram-negative rods that typically ferment glucose and are oxidase negative. *Serratia* species also usually reduce nitrate to nitrite and are Voges-Proskauer positive (128, 159). The mol% G+C content of DNA for *Serratia* species ranges from 52 to 60%, although the range in *S. fonticola* is 49 to 52% (159). In general, phenotypic systems such as the API 20E strip (bioMérieux), the Vitek 2 assay (bioMérieux), the Microscan Walk-Away test (Dade-Behring, Siemens), and the BD Phoenix test (BD Diagnostics, Sparks, MD) accurately identify several *Serratia* species, especially the most common species recovered from clinical specimens, *S. marcescens* and *S. liquefaciens*.

Members of the genus *Serratia*, save *S. fonticola*, can generally be differentiated from most members of *Klebsiella* and *Enterobacter* on the basis of gelatin and DNase activity (128, 159). There is, however, variation among the species of the genus *Serratia*, and phenotypic characteristics may have to be analyzed carefully, especially if a low-percentage identification is obtained with a system or kit.

Phenotypic Identification

Cultural and microscopic characteristics. *Serratia* species generally grow well on standard clinical laboratory media, such as tryptic soy agar with 5% sheep blood (SBA), chocolate agar, and MacConkey agar (MAC). Like those of other *Enterobacteriaceae*, colonies will typically be fairly large after overnight incubation, i.e., about 2 mm (159). These bacteria typically grow well at 30 to 37°C, although *S. plymuthica* may not grow well at 37°C (159, 160). Many *Serratia* species are able to grow at 4 to 5°C, but not *S. marcescens*, *S. rubidaea*, and *S. ureilytica* (36, 159). Nonpigmented strains will often be whitish to grayish, like many other *Enterobacteriaceae*, and tend to be round with entire margins.

The red pigmentation exhibited by many strains of *S. marcescens*, *S. plymuthica*, and *S. rubidaea* is probably the most striking feature of colonies of these organisms (Fig. 1). This red pigment, prodigiosin, is produced by many strains; however, nonpigmented clinical strains are commonly recovered from human specimens, and red-pigmented strains now tend to be environmental isolates (159). *S. nematodiphila* also produces red pigment, but it has not yet been isolated from human specimens (425). The other *Serratia* species do not produce prodigiosin. Prodigiosin, a prodiginine molecule, is a tripyrrole bioactive secondary metabolite that is bound to the cell envelope (32, 159). There are four main classes of prodiginines, and *S. marcescens*, *S. plymuthica*, and *S. rubidaea* produce a group 1 molecule, prodigiosin (410). Other organisms besides *Serratia* species produce prodigiosin, including other Gram-negative bacteria, such as *Pseudomonas magnesorubra* and *Vibrio psychroerythreus* (410). The physiological role of prodigiosin is unclear, but the molecule has antibacterial and antifungal properties (32). Interestingly, prodigiosin and other prodiginines are currently being investigated as immunosuppressive agents and anticancer agents, as these compounds have immunomodulatory capabilities (410). As a secondary metabolite, prodigiosin is produced in the later stages of growth and is

sensitive to several environmental factors, including temperature, pH, the availability of light, the amount of oxygen present, and the availability of inorganic ions, various amino acids, and carbohydrates (32, 159, 410). Thus, the pigment may not be produced by particular strains unless certain environmental conditions are met.

Prodigiosin-producing strains of *S. marcescens* belong to biogroups A1, A2, and A6 (159). *S. marcescens* strains that belong to nonpigmented biogroups such as A5 and A8 are frequently isolated from human specimens; ubiquitous, environmental strains often belong to biogroups A3 and A4 (159). Nonpigmented strains recovered from human clinical specimens started appearing in the late 1950s and were readily recognized by the early to mid-1960s (81, 127, 161, 231). The pigment may be red, pink, magenta, or orange, depending on cultural conditions, and colonies may be pigmented entirely or partially (159). Figure 1 shows the same *S. marcescens* strain inoculated onto MAC (Fig. 1A), trypticase soy yeast agar (TSY) (Fig. 1B), and sheep blood agar (Fig. 1C). The colonies of this particular isolate on MAC are bright red, and they are more orange on TSY. It is important that bench technologists do not confuse the red-pigmented colonies on MAC with lactose fermentation. Prodigiosin is a nonsoluble pigment, so it does not diffuse in agar. When cultures of *S. marcescens*, *S. plymuthica*, and *S. rubidaea* are incubated at 37°C, pigmentation may not appear, but it may form at 30°C (160).

Occasional strains of *S. marcescens* biogroup A4 produce another pigment, pyrimine (159). Pyrimine has been described as both pink (159) and reddish violet (195). Pyrimine contains ferrous iron and may have properties that mimic those of superoxide dismutase (195).

Some *Serratia* species also produce particular odors when cultured on solid media. A potato-like odor is produced by *S. ficaria*, *S. odorifera*, and some strains of *S. rubidaea* (141, 165, 167). The potato-like odor is due to pyrazines produced by these species (141). In addition, all of the other *Serratia* species are sometimes described as having a fishy-urinary odor due to trimethylamine and/or ammonia production (159).

Cells of *Serratia* are microscopically rod-like with rounded ends and range from 0.9 to 2.0 μm in length and from 0.5 to 0.8 μm in width (159). Like some other members of the *Enterobacteriaceae*, they may have a bipolar, or "safety pin," appearance on Gram staining, where the ends of the cells stain darker than the middle. Most strains of all *Serratia* species are motile, typically with peritrichous flagella (159), although *S. nematodiphila* has a single polar flagellum (425).

Identification of *S. marcescens*. *S. marcescens*, the species most likely to be recovered from clinical specimens, is well known as one of the few members of the *Enterobacteriaceae* that produces DNase, lipase, and gelatinase (128, 159). *S. marcescens* does not usually ferment lactose, although pigmented strains may initially appear to be lactose fermenters on MAC without a precipitate around colonies (Fig. 1A). *S. marcescens* does not produce indole, is lysine and ornithine decarboxylase positive, and is arginine dihydrolase negative. In addition, *S. marcescens* ferments sucrose and D-sorbitol but does not ferment L-arabinose or raffinose. *S. marcescens* can be differentiated from pigmented strains of both *S. rubidaea* and *S. plymuthica* by ornithine decarboxylase activity and a lack of L-arabinose and raffinose fermentation. There are several *S.*

marcescens biogroups and biovars; their differential characteristics are summarized in the current edition of *Bergey's Manual of Systematic Bacteriology* (159). See Table 5 for a selected list of characteristics useful for identifying *S. marcescens* and other *Serratia* isolates to the species level.

Identification of *Serratia* species. In addition to *S. marcescens*, most strains of species of the genus *Serratia* are positive for DNase production and gelatin hydrolysis (128, 159). *S. fonticola* is negative for these tests, though, is Voges-Proskauer negative, and is phenotypically much different from other *Serratia* species (145). Except for many strains of *S. odorifera*, *Serratia* species do not usually produce indole (128, 159), and only *S. ureilytica* and *S. glossinae*, both of which have not been implicated in human infections, produce urease (36, 146). Most strains of all species utilize citrate, hydrolyze esculin, hydrolyze corn oil (lipase), and are H₂S negative (128, 159, 425). *S. odorifera* is the only species that does not hydrolyze Tween 80 (159). There are also general patterns of carbon source utilization for the genus. Most strains of each species utilize maltose, D-mannitol, D-mannose, and trehalose, while dulcitol is not utilized by any species except for *S. fonticola* (128, 159). There are biotypes of *S. entomophila*, *S. grimesii*, *S. liquefaciens*, *S. odorifera*, *S. proteamaculans*, *S. quinivorans*, and *S. rubidaea*, and differential characteristics for these biotypes are listed in the current edition of *Bergey's Manual of Systematic Bacteriology* (159). See Table 5 for selected phenotypic characteristics for each *Serratia* species; for more complete characteristics, consult the current editions of *Bergey's Manual of Systematic Bacteriology* (159) and the *Manual of Clinical Microbiology* (128) and the papers with descriptions of *S. ureilytica* (36), *S. glossinae* (146), and *S. nematodiphila* (425). A brief summary of key characteristics of *Serratia* species (except for *S. marcescens*) follows.

(i) ***S. liquefaciens*.** *S. liquefaciens* isolates are not pigmented and produce DNase, gelatinase, and lipase. Most strains are lysine decarboxylase and ornithine decarboxylase positive. *S. liquefaciens* strains are indole, urease, and arginine dihydrolase negative. This organism is part of the *S. liquefaciens* complex, along with *S. grimesii*, *S. proteamaculans*, and *S. quinivorans*.

(ii) ***S. grimesii*.** *S. grimesii* is part of the *S. liquefaciens* complex and is not pigmented. Isolates produce DNase, gelatinase, and lipase and are arginine dihydrolase, lysine decarboxylase, and ornithine decarboxylase positive. *S. grimesii* ferments lactose.

(iii) ***S. proteamaculans*.** *S. proteamaculans* is in the *S. liquefaciens* complex. It is not pigmented and produces DNase, gelatinase, and lipase. It is lysine decarboxylase and ornithine decarboxylase positive. *S. proteamaculans* is indole, urease, and arginine dihydrolase negative.

(iv) ***S. quinivorans*.** Like *S. liquefaciens*, *S. grimesii*, and *S. proteamaculans*, *S. quinivorans* is in the *S. liquefaciens* complex. *S. quinivorans* produces DNase, gelatinase, and lipase. It is not pigmented and is indole, urease, and arginine dihydrolase negative. *S. quinivorans* is lysine decarboxylase and ornithine decarboxylase positive.

(v) ***S. ficaria*.** *S. ficaria* colonies are nonpigmented and produce a potato-like odor. This organism produces DNase, gelatinase, and lipase. *S. ficaria* isolates are indole, urease, arginine dihydrolase, lysine decarboxylase, and ornithine decarboxylase negative.

TABLE 5. Phenotypic characteristics of members of the genus *Serratia*^a

Characteristic	<i>S. marcescens</i>	<i>S. liquefaciens</i>	<i>S. grimesii</i>	<i>S. proteamaculans</i>	<i>S. quinivorans</i>	<i>S. ficaria</i>	<i>S. fonticola</i>	<i>S. rubidaea</i>	<i>S. odorifera</i>	<i>S. plymuthica</i>	<i>S. entomophila</i>	<i>S. glossinae</i>	<i>S. nematodiphila</i>	<i>S. ureilytica</i>
DNase	+	+	+	+	+	+	-	+	+	+	+	ND	+	ND
Gelatinase	+	+	+	+	+	+	+	+	+	+	+	-	+	ND
Lipase (Tween 80 hydrolysis)	+	+	+	+	+	+	+	+	+	+	+	ND	+	+
Lipase (corn oil hydrolysis)	+	+	+	+	+	+	+	+	+	+	+	ND	+	ND
Prodigiosin production	V	-	-	-	-	-	-	V	+	V	-	-	+	-
Potato odor	-	-	-	-	-	-	-	V	-	-	-	-	-	-
Indole	-	-	-	-	-	-	-	-	-	-	-	+	-	-
Urease	-	-	-	-	-	-	-	-	-	-	-	+	-	+
Arginine dihydrolase	+	+	+	+	+	+	+	V	+	+	+	+	+	+
Lysine decarboxylase	+	+	+	+	+	+	+	-	V ^b	-	-	+	+	+
Ornithine decarboxylase	+	+	+	+	+	+	+	-	+	-	-	+	+	+
L-Arabinose fermentation	-	-	-	-	-	-	+	+	+	+	+	+	+	-
D-Dulcitol fermentation	-	-	-	-	-	-	+	+	+	+	+	+	+	ND
Lactose fermentation	-	-	-	-	V	V	+	+	+	+	+	+	+	+
D-Sorbitol fermentation	-	-	-	-	V	V	+	+	+	+	+	+	+	+
Sucrose fermentation	+	+	+	+	+	+	V	+	V ^b	+	+	+	+	+

^a Characteristics were compiled from several references (36, 128, 146, 159, 425). ND, not determined; V, variable reaction.
^b *S. odorifera* biotype 1 is ornithine decarboxylase positive and ferments sucrose, while biotype 2 is ornithine decarboxylase negative and does not ferment sucrose.

(vi) *S. fonticola*. *S. fonticola* differs from the other species in the genus because most strains ferment D-dulcitol and do not produce DNase and gelatinase. *S. fonticola* produces lipase, is not pigmented, and is indole and urease negative. This organism is lysine decarboxylase and ornithine decarboxylase positive, usually ferments lactose, and is arginine dihydrolase negative.

(vii) *S. rubidaea*. *S. rubidaea* may be pigmented, and some strains also have a potato-like odor. It produces DNase, gelatinase, and lipase and ferments lactose. *S. rubidaea* may be lysine decarboxylase positive but is arginine dihydrolase and ornithine decarboxylase negative. This organism is indole and urease negative and does not ferment D-sorbitol.

(viii) *S. odorifera*. *S. odorifera* does not produce pigment and has a potato-like odor. It produces DNase and gelatinase, but it is the only *Serratia* species that does not hydrolyze Tween 80. Some strains of *S. odorifera* are indole positive. This organism is urease negative and lysine decarboxylase positive and usually ferments lactose. There are two biotypes, and biotype 1 is ornithine decarboxylase positive and ferments sucrose; biotype 2 is ornithine decarboxylase negative and does not ferment sucrose.

(ix) *S. plymuthica*. Like *S. marcescens* and *S. rubidaea*, *S. plymuthica* may be pigmented. It produces DNase, gelatinase, and lipase and ferments lactose. *S. plymuthica* is indole, urease, arginine dihydrolase, lysine decarboxylase, and ornithine decarboxylase negative.

(x) *S. entomophila*. *S. entomophila* is not pigmented. *S. entomophila* produces DNase, gelatinase, and lipase but is indole, urease, arginine dihydrolase, lysine decarboxylase, and ornithine decarboxylase negative. In addition, it does not ferment L-arabinose, lactose, or D-sorbitol.

(xi) *S. glossinae*. Laboratory identification data on *S. glossinae* are limited, since characteristics for only one strain have been determined, and not all tests were performed (146). *S. glossinae* is not pigmented and is the only *Serratia* species that does not produce gelatinase; DNase and lipase production were not determined for this isolate. *S. glossinae* is urease positive and indole and arginine dihydrolase negative. This organism is lysine decarboxylase and ornithine decarboxylase positive. *S. glossinae* is the only *Serratia* species besides *S. odorifera* biotype 2 that does not ferment sucrose.

(xii) *S. nematodiphila*. As with *S. glossinae*, only one isolate of *S. nematodiphila* has been characterized (425). *S. nematodiphila* is red pigmented and is also fluorescent. It produces DNase, gelatinase, and lipase and is arginine dihydrolase, lysine decarboxylase, and ornithine decarboxylase positive. *S. nematodiphila* ferments lactose and is indole and urease negative.

(xiii) *S. ureilytica*. Only one isolate of *S. ureilytica* has been characterized, similar to both *S. glossinae* and *S. nematodiphila* (36). *S. ureilytica* produces lipase, but DNase and gelatinase were not tested. It is the only *Serratia* species besides *S. glossinae* that produces urease. This organism is arginine dihydrolase, lysine decarboxylase, and ornithine decarboxylase positive. *S. ureilytica* is indole negative, and like *S. marcescens* and *S. entomophila*, it does not ferment L-arabinose.

Molecular Identification

16S rRNA gene sequencing is a method that efficiently distinguishes *Serratia* species. Figure 2 shows a dendrogram of the 16S rRNA gene sequences of the current species in the genus

Serratia, constructed by the neighbor-joining method in MicroSeq software (Applied Biosystems). 16S rRNA gene sequences of type strains were obtained from GenBank and are up to date through July 2011. The GenBank accession numbers used in the construction of the dendrogram are listed next to the species in Fig. 2. Links to each *Serratia* species type strain 16S rRNA gene sequence are available at the List of Prokaryotic Names with Standing in Nomenclature website (<http://www.bacterio.cict.fr/s/serratia.html>).

16S rRNA gene sequencing will differentiate *Serratia* species, including the members of the *S. liquefaciens* group (Fig. 2). A comparison of the sequences used in the construction of the dendrogram in Fig. 2 reveals that *S. liquefaciens* and *S. grimesii* differ by 6 bases, and *S. proteamaculans* and *S. quinivorans* also differ by 6 bases. In both cases, 16S rRNA gene sequencing would provide enough discrimination to identify these organisms. 16S rRNA gene sequencing, however, probably does not differentiate between biotypes or biogroups of *Serratia* species, including those of *S. entomophila*, *S. grimesii*, *S. liquefaciens*, *S. marcescens*, *S. odorifera*, *S. proteamaculans*, *S. quinivorans*, and *S. rubidaea*. The definition of what level of sequencing discrimination defines a species has not been determined, although a 0.5% to 1% difference is often used (80). In order to identify *Serratia* species biotypes, the differential characteristics listed in the current edition of *Bergey's Manual of Systematic Bacteriology* may be used (159).

Since the more common species in the genus are typically identified well with phenotypic systems, 16S rRNA gene sequencing does not have to be used often in clinical laboratories to determine the identity of problematic organisms. However, if a low-percentage identity is obtained with a system, 16S rRNA gene sequencing is useful for identification of the *Serratia* species.

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