

# Microbiological and Clinical Aspects of Infection Associated with *Stenotrophomonas maltophilia*

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## INTRODUCTION

Following a lengthy period of uncertain taxonomic status, the nonfermentative gram-negative bacillus previously known as *Pseudomonas maltophilia* or *Xanthomonas maltophilia* has now been reclassified as *Stenotrophomonas maltophilia*, the sole member of the genus *Stenotrophomonas*. Despite reports in the earlier literature that the bacterium was of strictly limited pathogenicity, *S. maltophilia* has risen to prominence over the last decade as an important nosocomial pathogen associated with significant case/fatality ratios in certain patient populations, particularly in individuals who are severely debilitated or immunosuppressed. The spectrum of clinical syndromes associated with *S. maltophilia* infection continues to expand.

Despite this, little is known about virulence factors associated with the bacterium. In addition, there is still considerable uncertainty about the route(s) of acquisition of *S. maltophilia*. Although a number of sources in the hospital environment have been identified, strains isolated from these sites often differ from those obtained from clinical material. In addition, evidence from a small number of reported outbreaks indicates that person-to-person transmission may be an infrequent occurrence in the nosocomial setting.

The majority of strains of *S. maltophilia* are characterized by their resistance to many currently available broad-spectrum antimicrobial agents, including those of the carbapenem class. Although resistance to drugs of the  $\beta$ -lactam class has been extensively investigated, mechanisms which confer resistance to other agents have received comparatively little attention. Current methods of in vitro susceptibility testing manifest significant variations in observed results hampering the selection of optimal therapy for *S. maltophilia*-associated infection.

Moreover, in vitro susceptibility data frequently do not cor-

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relate with a successful clinical outcome. Management of infection is sometimes further complicated by the emergence of mutants exhibiting pleiotropic resistance. Accordingly, attempts have been made to identify combinations of antimicrobial agents which exhibit in vitro synergy against *S. maltophilia* and which may also prevent the emergence of resistance. Although some of these combinations appear promising in this respect they remain largely untested in the clinical setting.

## MICROBIOLOGY

### Taxonomy

*S. maltophilia* is the only member of the genus *Stenotrophomonas* (*Stenos*, Greek: narrow; *trophos*, Greek: one who feeds; *monas*, Greek: a unit, monad; i.e., a unit feeding on few substrates; and *malt*, Old English: malt; *philos*, Greek: friend; i.e., a friend of malt). The genus was proposed in 1993 by Palleroni and Bradbury (313) after many years of debate regarding the appropriate taxonomic position of this organism. The type strain was isolated in 1958 by Hugh from an oropharyngeal swab from a patient with an oral carcinoma (184) and named *Pseudomonas maltophilia* (185, 186). Subsequently, Hugh and Ryschenkow reclassified "*Bacterium bookeri*," which had been isolated from pleural fluid in 1943 by J. L. Edwards, as *P. maltophilia* (184). *Pseudomonas melanogena* isolated from Japanese rice paddies in 1963 was later recognized as *Pseudomonas maltophilia* (235), as were strains which had initially been characterized as *Pseudomonas alcaligenes* by Komagata (184, 234). Similarly, strains of *Alcaligenes faecalis* as described by Ulrich and Needham (418) were subsequently reclassified by Hugh and Ryschenkow (186) as *P. maltophilia*. Later, the use of DNA-rRNA hybridization techniques revealed the presence of five rRNA homology groups in the genus *Pseudomonas*, as it then was, and showed that the rRNA cistrons of the *P. maltophilia* type strain ATCC 13637 were most similar to those of three strains of *Xanthomonas* (314).

This information was used by Swings et al. in 1981 to propose that *P. maltophilia* be reclassified in the genus *Xanthomonas* as *X. maltophilia* (402). In addition, they cited several other factors to support their case. These included the guanine-plus-cytosine (G+C) content (*P. maltophilia*, 63 to 67.5%; *Xanthomonas*, 63 to 70%); comparative enzymology, particularly the absence of NADP-linked dehydrogenases; the occurrence of the same type of ubiquinones (*P. maltophilia* and *Xanthomonas* spp. both possess ubiquinones with eight isoprene units, whereas all other *Pseudomonas* strains possess nine units); and similar cellular fatty acid composition. A subsequent analysis of whole-cell proteins patterns (424) appeared to support this proposal. Additional evidence from isoelectric focusing studies of outer membrane esterase (87) confirmed that *P. betle* and *P. hibiscicola* were synonyms of *X. maltophilia* (383, 421). However, the proposed reclassification of *P. maltophilia* as *X. maltophilia* did not meet with universal approval (312), and the controversy about the taxonomic status of this bacterium in the genus *Xanthomonas* remained unresolved (53).

The controversy was partly because some of the evidence put forward by Swings et al. (402) was subsequently contradicted by the findings of later studies. During an extensive DNA-rRNA hybridization study of the genus *Pseudomonas*, different melting temperatures were reported for the same 27 strains of *Xanthomonas* used in the proposal of Swings et al., despite the use of identical experimental conditions and the same *X. campestris* type strain as reference rRNA (96). The range for *X. maltophilia* was 76.5 to 78°C, almost overlapping the range for the genus *Xanthomonas* reported by Swings et al. (78.8 to

81.5°C) but further removed from that (80.0 to 81.5°C) reported later by De Vos and De Ley (96). In addition, Yang et al., using polyamine and fatty acid analysis (460, 461), demonstrated that *X. maltophilia* possessed profiles distinct from other species within the genus *Xanthomonas*. Furthermore, the possession of ubiquinones with eight isoprene units was shown not to be limited to *X. maltophilia* and other members of the genus *Xanthomonas* by Oiyazu and Komagata, who cited that they were found in several other pseudomonads including *P. avenae* and *P. palleroni* of rRNA group III (311).

These factors, along with supplementary evidence, were used to request a reinterpretation of the taxonomic position of *X. maltophilia* (425). This was supported by experiments with a *Xanthomonas*-specific 16S rDNA sequence as the primer for PCR (254). *Xanthomonads* were recognized by the presence of a single 480-bp PCR fragment; however, *X. maltophilia* strains produced additional PCR fragments, leading the author to conclude that *X. maltophilia* does not belong in the genus *Xanthomonas*.

Continuing dissatisfaction with the classification of this organism finally gave rise to the proposal in 1993 to create the new genus *Stenotrophomonas* with *S. maltophilia* as the sole member (313). More recently, Nesme et al. confirmed the distinction between *S. maltophilia* and members of the genus *Xanthomonas* by using restriction mapping of PCR-amplified 16S rRNA genes (293).

Recently, Drancourt et al. proposed a new species; *Stenotrophomonas africana*, which is biochemically identical to *S. maltophilia* except for its inability to assimilate *cis*-aconitate. Genotypic analysis, however, revealed only 35% DNA homology between the two species (104).

### Morphology, Culture Characteristics, and Growth Requirements

Cells of *S. maltophilia* are straight or slightly curved non-sporulating gram-negative bacilli that are 0.5 to 1.5  $\mu\text{m}$  long. They occur singly or in pairs and do not accumulate poly- $\beta$ -hydroxybutyrate as intracellular granules. They are motile by means of several polar flagella. The colonies are smooth, glistening, with entire margins and are white to pale yellow. Although Nord et al. (298) observed beta-hemolysis in 11 of 31 strains they examined, the bacterium is not generally considered to be beta-hemolytic. However, on blood agar there may be a greenish discoloration of the medium around confluent growth (149). On clear media, some strains may exhibit a brownish discoloration. This phenomenon has been attributed to a secondary chemical reaction among extracellular products and is more intense when these strains are incubated at 42°C (183) or cultured on media with a high tyrosine content (41).

*S. maltophilia* is an obligate aerobe. Growth does not occur at temperatures lower than 5°C or higher than 40°C and is optimal at 35°C. Margesin and Schinner reported the isolation from an alpine environment of a strain of the bacterium which was capable of growth at 10°C (258). Methionine or cystine is required for growth by most but not all strains (193, 260).

### Biochemical Characteristics

The bacterium has been regarded as relatively metabolically inactive (395), but a variety of unusual substrates, including the aminoglycoside antibiotic streptomycin (127), may be metabolized (37, 39, 55, 191, 209, 244, 273, 291, 333, 398) and strains of the bacterium have been investigated for their potential use as biodegradative agents. Selected biochemical characteristics and microbiological reactions of *S. maltophilia* are shown in Table 1.

TABLE 1. Biochemical and other characteristics of *S. maltophilia*

Test	Reaction <sup>a</sup>
Indophenol oxidase	-
Catalase	+
Growth	
5°C	-
18°C	+
37°C	+
Motility	
18°C	+
37°C	v
Indole	-
Lysine decarboxylase	+
Ornithine decarboxylase	-
Methyl red	-
Voges-Proskauer	-
Hydrogen sulfide	-
Reduction of nitrate to nitrite	v
Citrate	v
Phenylalanine deaminase	-
β-Galactosidase (ONPG)	v
Hydrolysis	
Esculin	+
Gelatin	+
Tween 80	+
DNA	+
Starch	-
Urea	-
Carbon sources for growth	
Adonitol	-
Arabinose	-
β-Hydroxybutyrate	-
Cellobiose	v
Dulcitol	-
Glucose	+
Fructose	v
Galactose	v
Mannitol	-
Mannose	v
Rhamnose	-
Salicin	-
Sorbitol	-
Trehalose	-

<sup>a</sup> +, >85% strains positive; v, 16 to 84% strains positive; -, ≤15% strains positive. Data from references 186, 312, 313, and 395.

### Cellular Constituents and Antigenic Structure

Somatic O antigens and flagellar H antigens have been described (186). A total of 31 O antigens have been identified, and these have been used to type *S. maltophilia* in epidemiological studies (220, 374, 375). The structures of seven of these antigens, including O3, which represents the most frequently occurring serotype, have been determined (98, 292, 448–452). The repeating units of these antigens are all branched and contain between three and five saccharides including relatively uncommon moieties such as 6-deoxy-L-talose, 3-acetamido-3,6-dideoxy-D-galactose, and 4-acetamido-4,6-dideoxy-D-mannose. Cross-reactions with the O antigens of *S. maltophilia* and *Brucella* spp. have been reported (76). Cross-reactions with *Renibacterium salmoninarum* have also been observed (18, 57), and Orrison et al. reported nonreciprocal cross-reactivity between *Legionella pneumophila* and *S. maltophilia* (309). Preparations of the bacterium are also capable of agglutinating mouse, rabbit, and human spermatozoa (26).

Moss et al. investigated the cellular fatty acid composition of *S. maltophilia* and identified the presence of relatively large amounts (26% of the total) of a branched-chain 15-carbon fatty acid:13-methyltetradecanoic acid (282). In addition, they identified three additional branched-chain hydroxy-fatty acids, i.e., 2-hydroxy-9-methyldecanoic, 3-hydroxy-9-methyldecanoic, and 3-hydroxy-11-methyldecanoic acids, which they did not detect in a range of other bacteria examined (281). They suggested that the uniqueness of the fatty acid profile of *S. maltophilia* could be of value in the identification of the bacterium.

### Genetics

Little is known of the genetic structure of *S. maltophilia*. A gene of 1,362 bp encoding a 48.5-kDa chorionic gonadotrophin-like hormone has been sequenced (164, 166). This hormone bears an immunological resemblance to human chorionic gonadotrophin (hCG) (163, 165) (see below). The gene encoding the L1 β-lactamase of *S. maltophilia* (*blaS*) was cloned and expressed in *Escherichia coli* by Dufresne et al. (106) and has been sequenced by Walsh et al. (439). Very recently, the same group published the sequence of the L2 β-lactamase (440). The sequences of the *alkA* and *alkB* genes, which code for alkane hydroxylase and rubredoxin reductase, respectively, have also been determined (245). Of 18 strains of *S. maltophilia* analyzed in one study, 5 were shown to harbor plasmids (380), but further analysis was limited.

### Habitat

*S. maltophilia* is found in a wide variety of environments and geographical regions, including Antarctica (430), and occupies ecological niches both inside and outside hospitals. It has been isolated from a number of water sources including rivers, wells, a hypereutrophic lake, and bottled water (in which it may be responsible for altered organoleptic properties), and sewage (13, 167, 176, 183, 184, 185, 219, 288, 319). The bacterium has also been recovered from a variety of soil (44, 85, 127, 400) and plant rhizosphere environments, including grasses, sugarcane and palms (202), from wheat (203), cabbage, rape, mustard, corn (86), beet (86, 243), bananas, cotton, beans, tobacco (183), rice paddies (235), citrus plants (1), orchids (447), irises (25), legume inoculants which use nonsterile peat as a carrier (306), and stored timber (108). Iizuka and Komagata reported the isolation of *S. maltophilia* from oil brines and other related materials from oil fields in Japan (191). *S. maltophilia* will also grow on loofah sponges (51).

The potential use of *S. maltophilia* as a biological control agent in rhizosphere environments and against agricultural pests has been explored (31, 32, 112, 173, 232, 239, 242, 264, 382). Given the broad range of phytopathogenic fungi inhibited by the bacterium, it is not altogether surprising that *S. maltophilia* has recently been reported to inhibit the growth of human fungal pathogens such as *Candida* spp. and *Aspergillus fumigatus* (213). The proposal that the observed inhibition is due to pyrrolnitrin production (213) merits further investigation, although it has also been suggested that chitinolytic activity exhibited by the bacterium may be of importance in this respect (232). Recently, Jakobi et al. reported the production of maltophilin, a novel macrocyclic lactam agent with antifungal activity against saprophytic, phytopathogenic, and human isolates, by *S. maltophilia* (195). Food sources for the bacterium include frozen fish (186), milk (185, 201), poultry eggs (7, 469), and lamb carcasses (381). In the laboratory, the organism has been isolated from contaminated cell cultures (395) and an isolate of *S. maltophilia* contaminating Sephadex columns was reported to tolerate 1% sodium azide (48).

TABLE 2. Nosocomial sources of *S. maltophilia*

Source	Reference(s)
Blood-sampling tubes.....	129, 378
Central venous/arterial pressure monitors.....	129
Contact lens care systems.....	49, 103, 270
Deionized-water dispensers.....	455
Dialysis machines.....	130, 422
Disinfectant solutions.....	455
Hands of health care personnel.....	419, 433
Hydrotherapy pools.....	330
Ice-making machines.....	95, 342
Nebulizers and inhalation therapy equipment.....	274, 275
Necropsy specimens.....	330
Oxygen analyzers.....	230
Oxygen humidifier water reservoirs.....	61
Shaving brushes.....	305
Shower heads, sink traps, and water faucets.....	220, 363, 405
Sphygmomanometers.....	117
Ventilator circuits.....	255, 433

The bacterium has also been isolated from a wide range of nosocomial sources, which are listed in Table 2.

The possibility of *S. maltophilia* being found in the domestic setting, in contrast to hospitals, has received comparatively little attention. In their investigation of the prevalence of pseudomonads in the domestic environment of cystic fibrosis sufferers and of control families, Mortensen et al. recorded low rates of isolation (4 of 407 cultures) of *S. maltophilia*, although it should be noted that they did not use a selective medium specifically intended to recover this bacterium (280). This is significant, because isolation from environmental samples and other heavily contaminated materials can be enhanced by the use of selective media (44, 202, 216).

Although relatively little information is available on the ability of *S. maltophilia* to survive drying, Rosenthal reported that whereas the bacterium was frequently isolated from wet environments such as sink traps, recovery from dry sites such as hospital floors was very uncommon (363). This is in agreement with the findings of Moffet and Williams (274), who cultured *S. maltophilia* from various nosocomial water samples but noted that isolation of the bacterium from dry surfaces of respiratory therapy equipment was comparatively rare. Hirai (177) investigated the ability of a single clinical strain of *S. maltophilia* to survive when inoculated onto cotton lint and glass plates. On the former, viable bacteria could not be identified 7 h after inoculation; whereas on the latter, viable organisms were recovered after the same period of incubation although less than 1% of the initial inoculum survived. The *D* value (the time required for 90% reduction of the initial inoculum) for survival on glass plates was 2.4 h. Although the presence of proteins, such as bovine serum albumin, increased the survival of other gram-negative bacteria, this was not observed with *S. maltophilia* (177).

### Human Carriage

Few studies have investigated the carriage rate of *S. maltophilia* in humans. Isolation from feces was first reported by Hugh and Ryschenkow in 1961 (186). Using a selective medium, von Graevenitz and Bucher recorded a fecal carriage rate of 10.9% (14 of 128 samples) in outpatients with diarrheal illness or their contacts (436). Rosenthal, however, was unable to isolate *S. maltophilia* from the rectal swabs of 50 ambulatory nursing home patients (363), although it should be noted that their isolation medium was of poorer selectivity than the medium of von Graevenitz and Bucher.

In a small series of 12 patients with hematologic malignancy, Kerr et al. (215) reported a fecal carriage rate of 33%. In contrast, only 2 of 69 (2.9%) subjects in a control group were fecal excretors of *S. maltophilia*. There have been few systematic studies of carriage rates at sites other than the lower gastrointestinal tract. Although carriage on the hands of health care workers during nosocomial outbreaks of *S. maltophilia* infection has been noted (419, 433), Khardori et al. (220) were unable to isolate the bacterium from skin swabs taken from hospital personnel. *S. maltophilia* has been isolated from the oropharyngeal swabs of healthy adults (183), although another study examining 200 throat or pharyngeal washings from healthy individuals participating in a health-screening program did not reveal the presence of the bacterium in any sample (363). Similarly throat swabs from hospital staff taken during the investigation of the nosocomial outbreak, reported by Khardori and colleagues, did not yield the bacterium (220). Respiratory tract carriage rates in individuals with cystic fibrosis are discussed in the section on respiratory tract infection, below. Carriage rates of 0% were recorded for 50 skin swabs of patients attending a cancer-screening clinic and for 50 vaginal swabs taken from gynecology clinic attendees (363).

Even less is known about animal sources of *S. maltophilia*. The bacterium has been isolated from fish, raw cows' and ewes' milk, rabbit feces (186, 248), lizards, frogs (183), the mouths and cloacae of captive snakes (105), and the gastrointestinal tracts of laboratory animals (135, 410). The bacterium has also been implicated in fleece rot of sheep (253). Lysenko and Weiser reported the recovery of *S. maltophilia* from the nematode *Neoplectana carpocapsae* (252).

Following the isolation of *S. maltophilia* from the ovarian fluid of a sow, Richert and Ryan (353) and others (2) demonstrated that the bacterium was capable of binding hCG. Subsequently, it was shown that an hCG-like protein (xCG) from *S. maltophilia* has a high degree of homology with the  $\beta$  subunit of hCG (164). An autocrine and/or paracrine function for xCG has been suggested following observations that when added to growth media, it (and hCG) causes changes in both the cell growth cycle and bacterial morphology (65). The nucleotide sequence of the chorionic gonadotropin-like protein receptor has been published (164, 166).

### Virulence Factors

Little is known of the putative virulence factors of *S. maltophilia*. The failure to distinguish between colonization and infection has fostered the belief that *S. maltophilia* is an organism of very limited pathogenicity. These views may have been reinforced by studies in which cases of infection with the bacterium were not associated with an unfavorable clinical outcome. For example, in their review of 106 intensive care unit patients infected or colonized with the bacterium, Villarino et al. were unable to attribute the death of any patient directly to *S. maltophilia* infection (433). Gardner et al. (145) suggested that *S. maltophilia* was often associated with clinically overt infection only when acting synergistically with other pathogens. Early attempts to induce infection in an experimental animal model appeared to support the hypothesis that *S. maltophilia* does not cause serious sepsis when whole bacteria are administered intravenously to mice.

Although extracts of bacterial cultures were associated with some toxicity, it was less severe than that in similar preparations of strains of *E. coli* (160). Elaboration of a range of extracellular enzymes by *S. maltophilia*, including DNase, RNase, fibrinolysin, lipases, hyaluronidase, protease, and elastase, was described in several early reports (9, 42, 43, 52, 196,

TABLE 3. Isolation of *S. maltophilia* by blood culture systems

Device	No. of samples yielding growth/total no. (%)	Reference
Manual		
Isolator	0/1 (0)	339
	6/8 (75)	174
	11/12 (92)	226
	18/19 (95)	227
Septi-Chek	5/12 (42)	226
Signal	0/3 (0)	81
	1/2 (50)	396
Semiautomated		
BACTEC radiometric	3/3 (100)	81
Continuous monitoring		
BacT/Alert	3/6 (50)	338
	6/8 (75)	174
BACTEC 9240	1/6 (17)	338
	1/1 (100)	339
ESP	9/19 (47)	227
o.a.s.i.s.	2/2 (100)	396

298, 302, 303, 377), and Bottone et al. have proposed that these enzymes may play a role in the pathogenesis of *S. maltophilia*-associated infection (52). They reported a case of ecthyma gangrenosum in a leukemic patient with *S. maltophilia* bacteremia. Because bacterial production of protease and elastase is deemed important in the pathogenesis of cases of ecthyma gangrenosum associated with *P. aeruginosa* septicemia, they examined the *S. maltophilia* isolate for elaboration of these enzymes and found that it was an "avid protease and elastase producer" (52). A larger study of 52 strains of clinical and environmental origin examined the production of nine extracellular enzymes. No strain produced lecithinase, hyaluronidase, or chondroitin sulfatase, whereas all the strains produced protease and elastase. Elastase production was variable, but there was no significant difference between clinical and environmental strains. Although DNase, lipase, and fibrinolysin were produced by all strains at 20°C, clinical isolates were significantly more likely to produce these enzymes when grown at 37°C (409).

Adherence to plastic is considered an important property of bacteria commonly implicated in line-related colonization and infection, and strains of *S. maltophilia* of both clinical and environmental origin have been reported to adhere to several types of plastic materials including intravenous cannulae (214).

Recently Jucker et al. investigated the adherence of a strain of *S. maltophilia* to both glass and Teflon (200). They noted that adhesion to these negatively charged materials was promoted considerably by the positive charge manifested by this strain at physiologic pH.

The ability of *S. maltophilia* to survive and multiply within total parenteral nutrition and other types of intravenous infusions may also contribute to the pathogenesis of intravenous line-related infections (266, 323). Similarly, the ability of this bacterium to grow in dialysis fluids with the release of low-molecular-weight pyrogens, which are apparently different from endotoxin-like moieties as detected in the *Limulus* amoebocyte lysate assay, may be important in the pathogenesis of pyrogenic reactions during hemodialysis (138).

The role of a cell wall-associated immunoglobulin G binding protein in the pathogenesis of *S. maltophilia* infection (162) requires further investigation. Serum resistance is a phenomenon frequently exhibited by gram-negative bacteria associated with septicemia, and a study of a small number of strains of *S.*

*maltophilia* noted that clinical isolates were much more likely to exhibit this property than were environmental isolates (217).

Virulence factors of importance in the pathogenesis of *S. maltophilia*-associated pulmonary infection remain to be characterized. Grant et al. (158) were unable to demonstrate adherence of the bacterium to cultured hamster tracheal cells.

### Laboratory Isolation

*S. maltophilia* can be isolated quite readily from normally sterile sites on a wide range of commonly used solid media, including blood, heated blood, MacConkey, and cysteine lactose electrolyte-deficient agars. It will grow overnight at temperatures ranging from 20 to 37°C in air and will also grow in 5% CO<sub>2</sub>. Most blood culture systems are capable of growing *S. maltophilia* with various degrees of efficiency. Published evaluations are summarized in Table 3.

It is difficult to determine the relative merits of the various systems with respect to isolation of *S. maltophilia* because of the small numbers of strains in many studies. It should be noted, however, that *S. maltophilia* has been isolated from terminal subcultures (false negative) taken from a number of systems including Oxoid Signal (396), BACTEC NR 660 (297), BacT/Alert (357), and Difco ESP (278), although on most occasions other bottles within each set were positive. In one study, the Isolator system detected significantly more positive cultures ( $P < 0.01$ ) and more sepsis episodes ( $P < 0.02$ ) with *S. maltophilia* than did aerobic bottles of the Difco ESP system (227).

### Selective Media

A number of selective media have been developed for the isolation of *S. maltophilia* from clinical or environmental specimens likely to be contaminated with other bacteria. Early examples, such as mineral acetate lactate methionine agar were of relatively poor selectivity (363). Antimicrobial agents were added to later medium formulations in an attempt to improve this. Juhnke and Des Jardins developed *Xanthomonas maltophilia* selective medium for the isolation of *S. maltophilia* from soil and rhizosphere environments (202). This medium contains six antibacterial agents, i.e., cephalixin, bacitracin, penicillin G, novobiocin, neomycin, and tobramycin, and two antifungal agents, i.e., nystatin and cycloheximide. Maltose and bromothymol blue were also included to facilitate the identification of *S. maltophilia* colonies, which, because of acid production from maltose, appear as orange with a yellow halo (202). In an investigation into environmental reservoirs and hand carriage of *S. maltophilia* by health care personnel, Villarino et al. used tryptic soy agar supplemented with 5% sheep blood to which 5 µg of gentamicin per ml had been added, although no comparator medium was tested (433).

Several media which take advantage of the inherent resistance of *S. maltophilia* to carbapenems have also been developed. Imipenem added to blood or MacConkey agar has been used to isolate *S. maltophilia* from stool (436) and sputum (154) samples. MacConkey agar which incorporated imipenem at a concentration of 10 µg/ml was more inhibitory for some strains than was imipenem-blood agar (436). Khardori et al. (220) used MacConkey agar supplemented with 25 µg of imipenem per ml, which might have contributed to the low rate of isolation of *S. maltophilia* from environmental sources during their investigation of a nosocomial outbreak. The imipenem-containing medium of Bollet et al. (44) incorporates methionine, thus taking advantage of the requirement of most strains of the bacterium for this amino acid (193, 260). Media which contain imipenem as the sole selective agent may fail to inhibit

the growth of some organisms found in stool cultures, particularly *Enterococcus faecium* and *Candida* spp. These problems can be circumvented by the further addition of vancomycin and amphotericin B to imipenem-containing agar (216) and the use of a mannitol-bromothymol blue indicator system to facilitate the differentiation of *S. maltophilia* (which does not produce acid from mannitol) from other imipenem-resistant gram-negative bacteria. This medium was shown to enhance the isolation of *S. maltophilia* from sputum samples taken from patients with cystic fibrosis (92) and the feces of patients with hematological malignancy (216).

### Identification in the Clinical Laboratory

*S. maltophilia* can be identified in the clinical laboratory by standard biochemical and other tests (151) (Table 1). In addition, Townsend et al. suggested that in vitro synergism between aztreonam and clavulanic acid by using disks containing 30 and 10 µg of drug, respectively, can be used in the presumptive identification of the bacterium (412). Furthermore, several commercial products which are intended to aid in the identification of gram-negative non-fermentative rods have been tested for their ability to accurately identify *S. maltophilia* (19, 70, 110, 205, 228, 229, 263, 271, 304, 332, 352, 356, 385, 387, 394, 407, 435, 441). Details of studies which have examined the utility of these methods, including automated and semiautomated systems, for the identification of this bacterium are listed in Table 4.

The limited number of *S. maltophilia* strains used in many of these evaluations (e.g., the study of Varetas et al., in which a single strain was used [426]), however, precludes definitive conclusions about the relative abilities of each system with respect to correct identification of this particular organism. Where comparative studies have evaluated automated and nonautomated systems, there have been no significant differences in their ability to identify *S. maltophilia* (304, 356).

Given its erstwhile relative infrequency of isolation from clinical material and uncertain taxonomic status, it is perhaps not surprising that several early reports noted that the identity of *S. maltophilia* could be confused with that of other bacteria and that it had been misidentified as *Pseudomonas alcaligenes* (192), *Bordetella bronchiseptica*, and *Alcaligenes faecalis* (186). Later reports, however, emphasize that misidentifications still occur. One strain of *Pseudomonas stutzeri* was misidentified as *S. maltophilia* by the Radiometer Sensititre AP80 (394), an isolate belonging to *Flavobacterium* group IIB was misidentified by the Vitek AutoMicrobic system (385), and two isolates were misidentified as *Pseudomonas diminuta* by the PASCO MIC-ID system (352).

Misidentification of *S. maltophilia* can have important clinical and psychosocial implications. In a survey of 32 "*Burkholderia cepacia*" strains isolated from cystic fibrosis patients sent to the Canadian *Pseudomonas* Repository Laboratory, 3 were subsequently identified as *S. maltophilia* (59). Misidentifications of this type are of particular concern since 20% of cystic fibrosis patients colonized with *B. cepacia* are known to suffer a syndrome of pneumonitis, septicemia, and rapid clinical deterioration and thus its isolation is understandably viewed with great alarm by these patients and their care givers.

Conversely, some systems have misidentified other organisms as *S. maltophilia*. In an evaluation of the RapID NF Plus, one strain of *B. cepacia* needed additional biochemical tests before it could be correctly distinguished from *S. maltophilia* (229). In addition to methods which rely on the biochemical reactions for the identification of *S. maltophilia*, several other techniques have undergone evaluation. These include gas-liq-

uid chromatography (240), direct-probe mass spectrometry (343), and molecular methods. Zechman and Labows (468) used automated headspace concentration gas chromatography to identify *S. maltophilia* and were able to distinguish the bacterium from *P. aeruginosa*, *B. cepacia*, *P. fluorescens*, and *P. putida*. Veys et al. correctly identified 59 strains of *S. maltophilia* by the presence of three characteristic peaks consisting of 3-hydroxydodecanoate, 13-methyltetradecanoate, and 12-methyltetradecanoate (431). An automated gas-liquid chromatography system, the Microbial Identification System (Microbial ID, Newark, Del.), correctly identified 45 of 47 (96%) *S. maltophilia* strains tested, with the others being misidentified as *Xanthomonas campestris* (310).

Molecular methods for the identification of *S. maltophilia* have, to date, received comparatively little attention. By using single-strand conformation polymorphism electrophoresis of PCR-amplified 16S rRNA fragments, species-specific patterns for *S. maltophilia* have been observed (445). Tyler et al. (417) were able to distinguish between *S. maltophilia* and seven species of *Pseudomonas* by identifying differences in the sequences of 16S to 23S rDNA internal transcribed spacers.

### EPIDEMIOLOGY

Until relatively recently, *S. maltophilia* was considered an unusual organism to isolate in the diagnostic microbiology laboratory, despite earlier claims that it was the second most common nonfermentative gram-negative bacillus (after *P. aeruginosa*) isolated from clinical specimens (41, 157, 180, 363). Isolation rates have been increasing since the early 1970s. At the M. D. Anderson Cancer Center (Houston, Tex.), the rate of *S. maltophilia* isolations per 10,000 admissions rose from less than 2 in 1972 to 8 in 1984 (115), and in 1993 at that institution, the bacterium represented the fourth most common gram-negative pathogen recovered from clinical specimens (428). The annual isolation rate at the University of Virginia Hospital doubled from 7.1 to 14.1 per 10,000 patient discharges from 1981 to 1984 (279), and at the Mayo Clinic, the incidence rose from 12.8 in 1984 to 37.7 per 10,000 patient discharges in 1987 (262). At a 470-bed tertiary trauma referral hospital affiliated with the University of Utah School of Medicine (Salt Lake City, Utah), the median monthly rate of *S. maltophilia* infection and/or colonization from January 1988 to February 1989 was significantly higher than for January through December 1987 (18.3 versus 7.4 per 1,000 patient-days;  $P < 0.0001$ ) (433), although this rise was due in part to an epidemic on the shock-trauma intensive care unit during the former period. One report suggests that isolations have continued to rise in the 1990s: in a French hospital, there were 20 isolates of *S. maltophilia* in 1991, 24 in 1992, and 65 in 1993 (84). Given that advances in medical technology are likely to create an increased population of individuals with risk factors which predispose them to infection, the incidence of *S. maltophilia* infection is likely to increase (285). These risk factors are summarized in Table 5.

Detailed comparisons between studies which have analyzed predisposing factors are not possible for a number of reasons. These include variations in patient mix, criteria used to define infection, and statistical methods used to analyze data. It is noteworthy, however, that several of these—such as prior exposure to antimicrobial agents—have been consistently associated with *S. maltophilia* infection and that nearly all of them are indicative of patient debilitation. Nagai (287) noted that 39 of 82 (48%) patients from whom *S. maltophilia* was cultured had a neoplastic lesion at the site of isolation of the bacterium. He proposed that an altered microenvironment caused by an

TABLE 4. Commercial systems used to identify *S. maltophilia*

System	No. of strains correctly identified/total no. of strains tested (%)	Reference
API 20E	5/5 (100)	304
	19/19 (100)	356
API 20NE	16/17 (94)	441
	2/2 (100)	387
	7/7 (100)	263
API rapid NFT	26/30 (87)	228
AutoSCAN W/A	33/34 (97)	407
	5/5 (100)	304
	4/4 (100)	332
	4/4 (100)	435
Biolog	63/64 (98)	271
Biotest	1/1 (100)	387
Cobas Micro ID-E/NF	2/5 (40)	304
Crystal Enteric/Non-Fermenter	16/17 (94)	179
	16/17 (94)	441
	6/6 (100)	356
Minitex	33/33 (100)	70
Radiometer Sensititre AP80	24/25 (96)	394
RapidID NF Plus	30/30 (100)	229
Rosco	1/1 (100)	387
Titertek-NF	55/57 (96)	205
Uni-N/F Tek	30/30 (100)	228
Vitek AutoMicrobic	13/30 (54)	228
	3/4 (75)	435
	27/28 (96)	19
	5/5 (100)	304
	4/4 (100)	332
	19/19 (100)	356

aerobic glycolysis in neoplastic tissue could provide conditions favorable for the multiplication of certain microorganisms and went on to suggest that *S. maltophilia* infection in a patient without other predisposing factors should prompt the diagnostic possibility of an associated malignant lesion (287).

Although antecedent therapy with carbapenems, to which the bacterium is inherently resistant, has been cited by several authors as a risk factor (21, 56, 60, 97, 99, 107, 116, 139, 189, 414, 453), it is not a prerequisite for colonization or infection. Indeed, other investigators have highlighted many cases of *S. maltophilia* infection where patients had received broad-spectrum antibiotics other than imipenem, such as aminoglycosides, fluoroquinolones, and extended-spectrum cephalosporins (63, 187, 218, 241). Vartivarian et al., in a review of 114 patients with mucocutaneous and soft tissue infection, found no preponderance of infection in patients receiving imipenem (429). Similarly, in their series of isolates from lower respiratory tract specimens of 27 patients in intensive care units, Maningo and Watanakunakorn noted that although most of the patients had received multiple antimicrobial agents before *S. maltophilia* isolation, only 2 had received imipenem (257).

Heath and Currie (172), in their series of *S. maltophilia* infections from tropical Australia, observed a marked seasonal variation, with the peak in incidence occurring in the wet season. They postulated that this may follow an increased usage of ceftazidime and imipenem as therapy for *Burkholderia pseudomallei* and *Acinetobacter baumannii* infections, which are also more common at this time. This interesting hypothesis warrants further investigation.

Several nosocomial outbreaks of *S. maltophilia* infection and/or colonization have now been described (36, 61, 67, 84, 128, 130, 147, 220, 241, 308, 342, 369, 416, 419, 422, 433, 455, 462). In several instances, putative environmental reservoirs for the bacterium have been identified. Contaminated deionized water used to make up disinfectant was found to be the source of one *S. maltophilia* outbreak which involved 63 patients in an Australian hospital (455). Four cases of septicemia with *S. maltophilia* were attributed to inadequate disinfection of reusable capillary dialyzers (422). Dialyzer effluents were contaminated with  $>10^4$  CFU of *S. maltophilia* per ml and had extremely low formaldehyde concentrations of between 0.0014 to 0.005% (against the expected 4%). Eight patients (four with leukemia, four with multiple myeloma) on a hematology ward developed infection with *S. maltophilia*, whose source was traced to an ice-making machine (342). The ice was used for making cold drinks and contained high levels of *S. maltophilia* ( $>10^5$  CFU/ml).

#### Typing Schemes

A variety of typing schemes have been developed in an attempt to elucidate the epidemiology of infections caused by *S. maltophilia*, and they have been used, with various degrees of success, to investigate nosocomial outbreaks. Phenotypic methods include serotyping based on heat-stable O antigens (220, 374, 375, 433) and lipopolysaccharide typing (12).

Typing based on comparison of antibiograms is of limited applicability because of a lack of variation in resistance patterns expressed by most strains (419). Similarly, biotyping is poorly discriminative because of a paucity of interstrain variability manifested by the bacterium. More recently, genotypic typing techniques have been the subject of much attention. Methods evaluated have included ribotyping (36, 114, 147), pulsed-field gel electrophoresis (PFGE) (241, 369, 405, 419, 462), random amplification of polymorphic DNA (RAPD) (67, 84, 419, 462), and enterobacterial repetitive intergenic consensus PCR (ERIC-PCR) (67). Other techniques which have been used to study the epidemiology of *S. maltophilia* are pyrolysis mass spectrometry (308) and multilocus enzyme electrophoresis (376).

An outbreak involving 45 patients on a shock-trauma intensive care unit was investigated by serotyping (433). Of 22 patient isolates available for typing, 19 (86%) were of serotype 10. A total of 11 of 17 samples from inanimate environmental sites (including respirometers, a tracheal suction catheter, components of a ventilation circuit, and water from a sink) and 3 of 6 hand cultures from nurses and respiratory therapists were positive for *S. maltophilia*. Of these 14 isolates, 13 were also of serotype 10. Reemphasis of the importance of hand washing before and after all patient contact, implementation of secretion and drainage precautions for all patients with *S. maltophilia* would infection, the use of gloves when suctioning or manipulating the respiratory tracts of ventilated patients, and high-level disinfection of respirometers between use in different patients were the measures used to successfully bring an end to the outbreak.

Serotyping was also used to analyze 52 clinical isolates col-

TABLE 5. Risk factors associated with *S. maltophilia* infection

Risk factor	References
Prior antibiotic therapy.....	115, 116, 145, 172, 187, 220, 238, 241, 284, 429, 432, 433, 470
Presence of a central venous catheter.....	115, 116, 220, 238, 284, 432
Neutropenia or cytotoxic chemotherapy.....	115, 116, 220, 238, 284, 301, 429
Prolonged hospitalization.....	116, 220, 238, 241, 429
Admission to an intensive care unit.....	172, 241, 279
Mechanical ventilation or tracheotomy.....	145, 172, 220, 241, 433
Underlying disease <sup>a</sup> .....	132, 196, 241, 279, 284, 358
Nonhematologic malignancy.....	196, 284, 287
Hematologic malignancy.....	220, 284, 429
Corticosteroid therapy.....	284, 433
Exposure to patients with <i>S. maltophilia</i> wound infection.....	433
Transportation to hospital by airplane.....	433

<sup>a</sup> Includes hepatobiliary, chronic pulmonary, and cardiovascular disease; organ transplantation; dialysis; intravenous drug use; and infection with the human immunodeficiency virus.

lected from 35 cancer patients over a 6-month period (220). Again, serotype 10 was the most common type (16 of 52 isolates [31%]). Eight other types were found among the remaining 36 isolates. Three environmental isolates were found on the medical intensive care unit, two of which were from water faucets and one was from a water sample. One of these belonged to serotype 10. The number of *S. maltophilia* isolates decreased following the earlier introduction of appropriate antibiotic therapy for *S. maltophilia* infection and an increase in the temperature of the boiler for hot water from 40 to 43.3°C. In a more recent study, Schable et al. examined 900 isolates from 10 countries and noted that 795 (88.3%) were serotypable. The most common serotypes were 10, 3, and 19 respectively, and they were predominantly associated with respiratory and blood isolates (375). This typing system is, however, of limited applicability because reagents are not widely available and because, as shown in the study of Schable et al., more than 10% of isolates are untypable. In addition, this method appears less discriminatory than other techniques (376).

The technique of pyrolysis mass spectrometry relies on the analysis of the products of thermal degradation of materials (337). It was used to investigate a suspected outbreak of *S. maltophilia* cross-infection and colonization on a heart-lung transplant intensive care unit (308). The respiratory tracts of five patients became colonized or infected over a 19-day period. All five had been nursed in either of two single cubicles equipped with positive-pressure ventilation. Extensive environmental sampling failed to reveal a source of *S. maltophilia*, although unauthorized reuse of "single-use" disposable nebulizers was uncovered. These had been cleaned but not resterilized. Twelve "cleaned" nebulizers were sampled prior to their intended reuse, and *S. maltophilia* was cultured from one of them. Although the five patient strains and the nebulizer strain were all different, the authors considered the outbreak to be related to reuse of disposable nebulizers, and the outbreak ceased when this practice was terminated.

Ribotyping has been used in the investigation of cases of nosocomial *S. maltophilia* bacteremia which occurred over 13 months in seven patients residing on four different wards of a pediatric hospital (36). Four patients (three on a gastroenterology ward, one on the intensive care unit) had the same ribotype, although the mode of transmission between these patients was not readily apparent. Ribotyping was also used to characterize 77 consecutive clinical *S. maltophilia* isolates in a Danish hospital (147). Great diversity was found among the ribotypes of the hospital strains, and no single-strain outbreak was detected. Potential reservoirs for these strains were not

determined. Wust et al. (458) used ribotyping to demonstrate that increasing antimicrobial resistance in serial isolates of *S. maltophilia* from a patient with cystic fibrosis was due to acquisition of resistance by the original strain rather than infection by other strains.

Several reports evaluating the usefulness of PFGE have been published. Thirty *S. maltophilia* strains from three countries (Brazil, Switzerland, and the United States) were analyzed by PFGE of *Xba*I or *Spe*I digests (369). With the exception of four strains from Brazil collected during an outbreak on a dialysis unit, all the strains were unrelated. Additional details relating to the Brazilian outbreak were, unfortunately, not given.

Ten strains from five patients and two environmental strains relating to a *S. maltophilia* outbreak on a hematology unit were examined by PFGE following chromosomal DNA digestion with *Dra*I (405). The five patients each had unique strains; however, the environmental isolates, one from a kitchen water faucet and one from a shower head, each matched the profile of one of the patient isolates.

PFGE following *Dra*I digestion was also used to analyze 109 clinical strains collected over a 10-month period in a Canadian hospital (462). This revealed 62 unique DNA restriction profiles. Respectively, 23, 11, 6, 6, and 3 strains had concordant profiles in each of five types. Four profiles were seen among 8 strains (2 strains with each profile), and the remaining 52 strains had unique profiles. Two profiles accounted for 32 (61.5%) of the 52 isolates from the intensive care units but only for 2 of 31 ward isolates. This was suggestive of nosocomial transmission of these two strains on the intensive care units but no details of any further investigations were given.

PFGE of *Xba*I or *Ssp*I digests of chromosomal DNA was used to examine 64 clinical *S. maltophilia* isolates collected from 60 patients and the hands of one nurse over a 9-month period (419). Eight of the patients and the nurse were involved in an outbreak of *S. maltophilia* on an intensive care nursery. Although isolates from six of the eight patients had the same profile, the isolate from the hands of the nurse was unique. Turner-Hubbard et al. (416) used *Spe*I-based PFGE to demonstrate that isolates from bronchoalveolar lavage fluid were indistinguishable from those from bronchoscopes which had undergone defective sterilization procedures. More recently, Fabe et al. used this technique after *Xba*I or *Dra*I digestion to examine strains from a hematology unit. They observed great genomic diversity among the strains analyzed but reported that person-to-person spread had occurred between several patients (117). An investigation into pulmonary colonization in cystic fibrosis patients by PFGE failed to demonstrate evidence

of a common source of exposure or person-to-person spread among five patients (437).

RAPD, also known as arbitrarily primed PCR and multiple arbitrary amplicon profiling, has also been reported to be a useful tool for typing *S. maltophilia*. Its advantage over PFGE is that it is a more rapid and less labor-intensive method. However, there have been disagreements about which is the more discriminatory (420, 462).

RAPD as a single typing method has been used to type 130 *S. maltophilia* strains (51 from the hospital environment, 48 clinical, and 31 from other environments) collected over an 8-month period in a French hospital (84). Sixteen cases where pairs were indistinguishable by RAPD profiles were identified: nine clinical, five from the hospital environment, and two from soil. Some evidence of cross-infection between hematology and intensive care unit patients was identified, but there were no matches between environmental and clinical strains.

ERIC-PCR has also been used to successfully type *S. maltophilia* (67). A total of 38 clinical strains were examined, 9 from a burn unit, 20 epidemiologically unrelated isolates, and 9 from the same cystic fibrosis patient. The burn unit strains and the 20 other unrelated strains were independent. The nine strains collected from the sputum of the cystic fibrosis patient over a 22-month period were, however, indistinguishable. The authors compared ERIC-PCR with RAPD. Both yielded rapid, reproducible, and discriminatory fingerprints of *S. maltophilia*. However, the authors were of the opinion that interpretation of results was easier with ERIC-PCR.

Schable et al. used multilocus enzyme electrophoresis, in conjunction with serotyping, to investigate an outbreak of *S. maltophilia* infection on a shock-trauma intensive care unit (376). Although most of the outbreak strains belonged to serotype 10, strains of this serotype unrelated to the outbreak yielded different electrophoretic types on multilocus enzyme electrophoresis (376).

Despite the number of reported outbreaks in which there was identification of clusters of strains indistinguishable on typing (36, 369, 419, 433, 462), exact sources and modes of transmission of *S. maltophilia* have proved difficult to elucidate. The great diversity of strains identified within given institutions (84, 147), the relative frequency of isolation from a wide variety of environmental sites, and the culture from some of these sites of strains indistinguishable from associated clinical strains (405) suggest that multiple independent acquisitions from environmental sources could be an important mode of transmission of *S. maltophilia*.

#### CLINICAL MANIFESTATIONS OF *S. MALTOPHILIA* INFECTION

*S. maltophilia* is associated with an ever-expanding spectrum of clinical syndromes. However, many early publications failed to cite unequivocal evidence for infection with this organism. Indeed, the isolation of the bacterium in mixed culture, coupled with difficulties in distinguishing between colonization and true infection at superficial sites (such as skin ulcers or the upper respiratory tract) and the recovery of the bacterium as a contaminant of necropsy specimens (330), fostered the opinion expressed in earlier reports (145, 330, 390, 401) that *S. maltophilia* was an organism with strictly limited pathogenic potential which was rarely capable of causing disease in individuals other than those who were severely debilitated or immunocompromised. Holmes et al. considered that only 6 of 128 isolates submitted to a reference laboratory were associated with genuine infection (180). A more recent publication of a series of 68 patients from whom *S. maltophilia* was isolated

concluded that only 9 patients had clinical evidence of infection with this organism (187). However, more recent studies that used stringent criteria for defining infection, coupled with isolation of the bacterium from normally sterile sites, have established beyond doubt that *S. maltophilia* can behave as a true pathogen. Although *S. maltophilia* is regarded as being primarily a nosocomial pathogen (33, 118, 262, 392), community-acquired infection with this bacterium may occur more frequently than was previously recognized (109, 172, 265). For example, Laing et al., in their series of 63 patients presenting to three acute-care hospitals, reported that 15 (23.8%) cases of infection and/or colonization with *S. maltophilia* were community acquired (241). In another study, 26 (24%) of 109 isolates were deemed to have been acquired in the community (462), and Southern and Schneider noted that 50% of strains in their series of 32 patients were isolated at the time of admission or from outpatients (390). Of the seven reported cases of *S. maltophilia* meningitis, only three were nosocomial in origin (295).

#### Bacteremia

Bacteremia is a common manifestation of *S. maltophilia* infection (116, 134, 197, 220, 222, 238, 241, 279, 284, 285, 301, 432) and appears to be increasing in frequency (238). Bacteremia may be secondary to a pulmonary, urinary, or gastrointestinal source (8, 388, 467, 470) although it is often not possible to determine the portal of entry. The importance of intravascular devices in the pathogenesis of *S. maltophilia* bacteremia is, however, becoming increasingly recognized (10, 28, 78, 115, 116, 138, 279, 284, 432), and in cases where there is no obvious source of infection it has been suggested that these devices may be the primary source. For example, Muder et al. report that in their series of 91 patients with *S. maltophilia* bacteremia, 56% did not have a clinically apparent portal of entry but 84% of these individuals had a central venous catheter in place (284). In several instances, it has been possible to identify environmental reservoirs from which *S. maltophilia* was likely to have been acquired. Flaherty et al. (130) investigated an outbreak of gram-negative bacteremia, including three cases caused by *S. maltophilia* and an additional case from which both *S. maltophilia* and *Enterobacter cloacae* were isolated from blood cultures. The source was identified as contaminated O-rings in reprocessed hemodialyzers. High-level O-ring contamination during simulated dialysis was demonstrated by Bland et al. to produce blood compartment contamination with *S. maltophilia* (40). Inadequate disinfection during reprocessing of capillary dialyzers was also implicated in another outbreak of *S. maltophilia* bacteremia (422). A cluster of cases reported by Fisher et al. (129) traced the source to contaminated pressure monitoring systems during open-heart surgery.

It is important to distinguish true *S. maltophilia* bacteremia from pseudobacteremia (197) arising from contamination of blood cultures when samples used to fill tubes for coagulation studies (which contain nonsterile anticoagulants such as sodium citrate) are then used to inoculate blood culture bottles (8, 378). This may be a more frequent occurrence than is generally recognized (8).

Relapsing *S. maltophilia* bacteremia has been described (36, 115, 285). Molecular typing techniques demonstrated that blood culture isolates from a patient who had experienced three episodes of bacteremia were indistinguishable.

Case/fatality ratios associated with *S. maltophilia* bacteremia may be high (36, 115, 285). In a series of 32 cases, Jang et al. noted that 22 (69%) were associated with a fatal outcome; 13 (41%) of these were deemed to be directly attributable to

septicemia (197). Some investigators have also reported that polymicrobial bacteremia with *S. maltophilia* is a frequent occurrence (115). In their study, Jang et al. (197) noted that 44% of 32 cases of bacteremia were polymicrobial in origin. According to some investigators, the acute mortality rate associated with these polymicrobial bacteremias is not significantly different from that associated with bacteremia due to *S. maltophilia* alone (115, 197), although this is in contrast to the reports of others (238). *S. maltophilia* septicemia may be complicated by disseminated intravascular coagulation and purpura fulminans (208, 267). Ecthyma gangrenosum is also a well-recognized complication (52) (see the section on skin and soft tissue infection, below).

### Endocarditis

There have been several reports of *S. maltophilia* endocarditis (15, 100, 115, 128, 168, 180, 197, 285, 378, 389, 399, 456, 464, 467, 470). Most of the cases have occurred in intravenous drug abusers or as a complication of prosthetic valve surgery. In the latter, infection often arises early in the postoperative period, possibly due to contaminated vascular access devices (115), although late-onset infections have been described (100, 115). Semel et al. reported a patient being treated for streptococcal prosthetic valve endocarditis who developed *S. maltophilia* superinfection, which they attributed to reflux of contaminated anticoagulant from collection tubes into the patient's venous system (378). Endocarditis in the absence of drug abuse or cardiac valve abnormalities is uncommon (115, 389). For example, Gutierrez Rodero et al. described a case of endocarditis following infection of a ventriculoatrial cerebrospinal fluid (CSF) shunt in a patient with otherwise normal native cardiac valves (168). The prognosis of *S. maltophilia* endocarditis is variable. Although favorable outcomes with antimicrobial therapy alone have been recorded (168), surgical intervention to replace the infected valve may be necessary (467). The infection may be complicated by valve ring or myocardial abscesses and septic emboli (197, 285, 467).

A variety of other cardiovascular manifestations of *S. maltophilia* infection have been reported, including pericarditis (115, 470), infection of the pseudopericardial sac in an artificial heart recipient (101), and bacteremia in association with mitral valve prolapse (289).

### Respiratory Tract Infection

*S. maltophilia* has been reported to account for 5% of nosocomial pneumonias (3), although several large studies of the etiology of nosocomial pneumonia have failed to find any cases associated with this bacterium (77, 351, 411). Nosocomial pneumonia has been observed during outbreaks of *S. maltophilia* infection, with several cases occurring over relatively short periods (220, 241, 308, 433).

The respiratory tract is the most common site of isolation of *S. maltophilia* in hospitalized patients, accounting for the origin of 56 to 69% of isolates (84, 147, 241, 279), although the majority of patients (53 to 71%) with *S. maltophilia*-positive respiratory tract cultures are colonized rather than infected at this site (220, 241, 433). More rigorous diagnostic criteria are necessary, therefore, if the distinction between colonization and true infection is to be made (137).

*S. maltophilia* nosocomial pneumonia is associated with mechanical ventilation, tracheostomy, previous exposure to broad-spectrum antibiotics, the use of respiratory tract equipment such as nebulizers (116, 220, 233, 241, 279, 308, 433, 470), and therapy with aerosolized polymyxin (122). Many patients also have preexisting lung conditions such as chronic obstructive

pulmonary disease, bronchiectasis, kyphoscoliosis, or endobronchial obstruction (241, 247, 470). Pulmonary infection following lung transplantation has also been reported (465).

Respiratory tract involvement with *S. maltophilia* is associated with significantly increased mortality (279). Kollef et al. (233) reported that the isolation of a "high-risk" pathogen such as *S. maltophilia* was the most important predictor of mortality in late-onset ventilator-associated pneumonia. The mortality rate in neutropenic patients with pneumonia is 40% (220).

The source of *S. maltophilia* in these patients is often unclear (172). Although ventilator circuits have yielded the organism when sampled (255, 308, 433) this may have represented contamination from the patient rather than the source itself. Klick and Du Moulin (230) reported a cluster of cases on an intensive care unit in which an oxygen analyzer contaminated with *S. maltophilia* was implicated, and Korn et al. also described an outbreak associated with reusable in-line ventilator temperature probes (236). In their study, Turner-Hubbard et al. attributed the isolation of *S. maltophilia* from bronchoalveolar specimens to faulty bronchoscope sterilization protocols (416). Interestingly, they did not observe clinically overt infection as a result of using contaminated bronchoscopes.

Although several extensive studies of the etiology of community-acquired pneumonia have failed to identify a single case in which *S. maltophilia* was the cause (22, 54, 119, 120, 206, 261), a few cases of community-acquired pneumonia have been described (372); these mostly occurred in patients with predisposing conditions such as rheumatic heart disease and bronchiectasis (194, 388). The case reported by Irifune et al. is noteworthy because the isolate exhibited a mucoid phenotype (194). Gardner et al. (145) reported a case of *S. maltophilia* bacteremia secondary to aspiration pneumonia.

The first reported isolation of *S. maltophilia* from the respiratory tracts of patients with cystic fibrosis was in 1975 in Denmark by Frederiksen et al. (133). The prevalence of *S. maltophilia* in this patient group has been increasing, but variation between centers is well recognized. The prevalence rose from <2% in 1975 to 19% in 1993 in Denmark (133) and from 0% in 1983 to 10% in 1990 in one British center (154). It is now 19% in another British center (93) and over 30% in one Spanish center (16). The prevalence has generally been lower in the United States, ranging from 1.8 to 8.7% (89, 283). The reasons for this increase are not clear, but one study suggested that the amount of antipseudomonal antibiotics with which these patients were treated and the duration of hospitalization were important risk factors (154). *S. maltophilia* may persist for long periods in the sputum of patients colonized with the bacterium (24). Recently, in a comparison of four different methods for preculture treatment of sputum samples from cystic fibrosis patients, Hoppe et al. found no significant effect on *S. maltophilia* isolation rates (181), although the use of selective media may affect the ability of clinical laboratories to demonstrate the presence of the bacterium in sputum (92).

There is no evidence to date of any nosocomial transmission of *S. maltophilia* to cystic fibrosis patients (94, 437).

The prognostic significance of *S. maltophilia* in the respiratory tract of cystic fibrosis patients is unclear. Some studies have shown no evidence of an adverse clinical outcome (89), whereas others have reported progressive deterioration in pulmonary function, particularly in patients chronically colonized for long periods with bacterial counts of *S. maltophilia* in excess of  $10^5$  to  $10^6$  CFU/ml of sputum (16, 207, 231). For a more detailed discussion of *S. maltophilia* in cystic fibrosis, the reader is referred to the recent review by Denton (91).

Instances of true infection of the upper respiratory tract appear very rare. The clinical significance of the isolation of *S.*

*maltophilia* from pharyngeal swabs (185, 186, 401) is uncertain. Harlowe reported a single case of *S. maltophilia* acute mastoiditis in a patient who developed acute otitis media after swimming (170).

### Central Nervous System Infection

Meningitis caused by *S. maltophilia* is uncommon (183). In neonates and infants, the infections appear spontaneous in onset (90, 373), whereas those in adults are secondary to neurosurgical procedures (153, 285, 295, 415). The presence of foreign material such as CSF shunts, ventriculostomy tubes, and Ommaya reservoirs may be important in the pathogenesis of these infections (295). Additionally, a spinal epidural catheter was deemed to have predisposed a patient to the development of a spinal epidural abscess (438). Adult cases of *S. maltophilia* meningitis in the absence of antecedent neurosurgery are very rare (327). The recently proposed species, *S. africana*, as described by Drancourt et al., was isolated from the CSF of a human immunodeficiency virus-seropositive Rwandan refugee with clinical signs of meningoencephalitis (104).

### Ophthalmologic Infection

Ocular infections associated with *S. maltophilia* appear to be increasing in incidence (331). A variety of ophthalmologic syndromes have been reported, including conjunctivitis, keratitis, dacryocystitis, and preseptal cellulitis (28, 331, 373, 386, 390, 401). Conjunctivitis, keratitis, and corneal ulcers in contact lens wearers from whom the bacterium has been isolated have also been described (237, 331, 393). Chen et al. (68) reported a case of endophthalmitis following the implantation of a sustained-release preparation of ganciclovir. Endophthalmitis has also been described following cataract extraction (204). *S. maltophilia* has been isolated from contact lenses or lens care paraphernalia (73, 103, 211, 331), and it has been suggested that synergy between *S. maltophilia* and *Acanthamoeba* spp. may be important in the pathogenesis of contact lens-associated amebal keratitis (49, 50).

### Urinary Tract Infection

Although *S. maltophilia* has been frequently isolated from urine specimens, early reports acknowledged that there was insufficient evidence to support an unequivocal role for this bacterium as a urinary tract pathogen (145, 150, 180, 287, 401). Therefore, it has come to be considered an uncommon cause of urinary tract infection (470). In most patients, the infection is acquired in the hospital setting (241) and is usually secondary to urinary tract surgery or instrumentation, including catheterization (148, 220, 470), or against a background of structural urinary tract abnormality (428). Wishart and Riley (455) reported an outbreak of nosocomial infection in which the source was identified as a contaminated disinfectant used for bladder instillation. Community-acquired infection appears rare (265).

Peritonitis in patients undergoing chronic ambulatory peritoneal dialysis has been observed (29, 324, 403, 404). This may follow Tenckhoff cannula exit-site infection, although most *S. maltophilia* exit-site infections do not appear to progress to peritonitis (83).

Urethritis, periurethral abscess, and epididymitis have also been reported (150, 180, 401). Garcia et al. described the isolation of the bacterium from semen specimens from fertile men (140).

### Skin and Soft Tissue Infection

*S. maltophilia* is a relatively frequent isolate from wounds and other skin lesions (148, 150, 180, 220, 279, 390). However, a paucity of clinical details, coupled with incomplete information on microbiologic and other diagnostic criteria, often make it difficult to establish an unequivocal role for *S. maltophilia* as a pathogen in this context (250, 262, 330, 429), particularly when the organism is isolated in mixed culture. Improved diagnostic criteria may, in the future, allow the distinction between true infection and colonization (241).

Wound sepsis may follow accidental injury (148, 150, 330) including accidents in the workplace (4, 109, 155). Infection also occurs after surgical trauma (148, 150) and at sites where cutaneous defenses have been breached iatrogenically, such as tracheostomies and suprapubic (115), Tenckhoff, and vascular catheter sites (115, 429).

Primary and metastatic *S. maltophilia* cellulitis is reported increasingly from patients with solid-organ or hematologic malignancy. In a series of 114 cases of *S. maltophilia* infection in cancer patients, Vartivarian et al. reported 11 cases of cellulitis (429). Metastatic cellulitis may manifest as ecthyma gangrenosum. Although more commonly associated with *P. aeruginosa* bacteremia, this syndrome is a recognized feature in systemic *S. maltophilia* infection in oncology patients (52, 115, 197, 215, 285, 429). Recently, a syndrome of metastatic cellulitis associated with nodular skin lesions in individuals with leukemia has been described (429). These lesions may mimic disseminated fungal infections and are associated with a poor prognostic outcome. *S. maltophilia* is also associated with mucocutaneous and perineal lesions in patients with malignancy (287, 334, 429).

Other manifestations of *S. maltophilia* soft tissue infection include umbilical cellulitis (455), prepatellar bursitis (318), infections of burn wounds (210), cat scratches, and human bite wounds (390).

### Bone and Joint Infection

Bone and joint infections are uncommon. They may follow orthopedic surgery (148, 150, 172) or trauma (17). Sequeira et al. reported a case of pubic symphysis infection in an intravenous drug abuser from whom *S. maltophilia* and *P. aeruginosa* were isolated (379).

### Gastrointestinal Infection

Although asymptomatic fecal carriage of *S. maltophilia* has been noted in several reports (see the section on habitat, above), the bacterium appears to be an infrequent cause of gastrointestinal infection. Isolation from ascitic fluid and from intra-abdominal abscesses (including liver abscesses) has been recorded (102, 107, 286, 390), and five cases of cholangitis caused by *S. maltophilia*, all of which were secondary to biliary tract obstruction associated with malignancy, have also been described (317, 470). Zuravleff and Yu (470) cited a case of bacteremia subsequent to gastroenteritis, although it is unclear whether the two events were causally related. Minah et al. noted the appearance of *S. maltophilia* in the oral flora of cancer patients undergoing myelosuppressive chemotherapy, but they did not observe symptoms of acute infection in these individuals (272).

It has been suggested that cell wall defective variants of *S. maltophilia* may play a role in the pathogenesis of Crohn's disease and ulcerative colitis (321, 322). Graham et al. used DNA hybridization techniques to identify sequences with homology to *S. maltophilia* in patients with chronic inflammatory

bowel disease (CIBD) but concluded that the role of the bacterium in the natural history of CIBD has not been established unequivocally (158). Additional immunologic, serologic, and immunocytochemical evidence does not support its role in CIBD (190, 443, 444).

## MANAGEMENT OF *S. MALTOPHILIA* INFECTION

### In Vitro Susceptibility Testing

Infections caused by *S. maltophilia* are particularly difficult to manage because clinical isolates are frequently resistant to many antimicrobial agents (see below). These difficulties are compounded by methodological problems associated with susceptibility testing. Disk diffusion methods are deemed inaccurate and of poor reproducibility (178, 268, 315, 316, 462), with marked variations in results observed when zone diameters were measured after 24 and 48 h of incubation (315, 316). Quinolone agents, particularly ciprofloxacin, appear most problematic in this respect (20, 161, 316, 354), although Arpi et al. reported that disk diffusion was as reliable as Etest and agar dilution in determining the susceptibility of 124 clinical isolates of *S. maltophilia* to ciprofloxacin (11). In a study of 33 clinical isolates comparing agar dilution and disk diffusion tests, Hohl et al. (178) observed a 12% very major error rate and 58% minor error rate with ciprofloxacin. Although most workers have noted that erroneous disk diffusion tests overstate the activity of quinolones against *S. maltophilia*, false resistance has also been reported (161). The National Committee for Clinical Laboratory Standards currently recommends agar or broth dilution methods for *S. maltophilia* (290). These methods, however, are time-consuming, and alternative methods such as the Etest (AB Biodisk Solna Sweden) have been evaluated (316). Yao et al. compared the Etest with an agar dilution method by using 176 clinical isolates of *S. maltophilia* and reported an overall agreement of 94% between the two techniques (463), although Pankuch et al. noted that MICs of ticarcillin-clavulanate obtained with by technique did not correspond well to those obtained by four other methods (316).

A number of factors have been cited as affecting results of susceptibility testing. With respect to drugs of the  $\beta$ -lactam class, these include both the type (111) and nutrient concentration of susceptibility medium used (45). Hawkey et al. noted that the concentration of  $Zn^{2+}$  in the test medium influences the observed susceptibility of *S. maltophilia* to imipenem, although variations in  $Ca^{2+}$  and  $Mg^{2+}$  concentration had no such effect (171). A similar phenomenon was not observed for the  $Zn^{2+}$  concentration and meropenem (75). This observed effect does not appear to be mediated by a direct effect of the zinc ions on the zinc-dependent L1  $\beta$ -lactamase (see below) of *S. maltophilia* (46). Divalent cation concentrations have, however, been reported to affect the MICs of the carboxy- and ureidopenicillins (82, 124). Similar effects have been observed with tetracycline, polymyxin B, aminoglycosides, and trimethoprim-sulfamethoxazole (82, 124).

Tilton et al. observed differences in the MICs of gentamicin and tobramycin in a comparison of broth and agar techniques (408). The incubation temperature also influences the results obtained on susceptibility testing, with aminoglycosides and polymyxin B appearing less susceptible when the bacteria are incubated at 30°C (320, 365, 442).

### Resistance of Antimicrobial Agents

*S. maltophilia* is resistant to many currently available broad-spectrum antimicrobial agents. Particularly noteworthy is the

resistance to drugs of the  $\beta$ -lactam class. Initially, resistance to these agents was thought to be conferred by two enzymes designated L1 and L2 (370, 371). The former, produced by virtually all wild-type strains (329), belongs to the metalloenzyme family, although the deduced amino acid sequence shows significant differences from that of other enzymes of this class such as the  $\beta$ -lactamases produced by *Aeromonas hydrophila* and *Bacillus cereus* (126, 439). These enzymes are dependent on the presence of  $Zn^{2+}$  at the active site. Although the zinc moiety in L1 can be replaced by  $Co^{2+}$ ,  $Cd^{2+}$ , or  $Ni^{2+}$ , these enzymes are less active than the native enzyme (35). The holoenzyme, which consists of a tetramer of four equal subunits, hydrolyzes a broad range of drugs of the  $\beta$ -lactam class, albeit with different degrees of catalytic efficiency (125). It exhibits predominantly penicillinase activity, although it is unable to hydrolyze aztreonam. It has been the subject of much attention, however, because of its ability to hydrolyze carbapenems such as imipenem and meropenem. It is not susceptible to  $\beta$ -lactamase inhibitors, such as clavulanate, although Payne et al. have very recently reported the inhibition of L1, and other metallo- $\beta$ -lactamases by mercaptoacetic acid thiol ester derivatives (328). Following experiments with a purified enzyme from *Bacillus cereus*, they proposed that hydrolysis of these compounds by metallo- $\beta$ -lactamases yields mercaptoacetic acid, which forms a disulfide link with a cysteine residue at the active site (328). In contrast to L1, L2, which exists as a dimer in its native state, is an enzyme with a serine active site. Comparison of the amino acid sequence of L2 with other enzymes has shown that it is most closely related to the TEM  $\beta$ -lactamase (440). It exhibits principally cephalosporinase activity but also hydrolyzes aztreonam (370). Unlike L1, this enzyme is susceptible to  $\beta$ -lactamase inhibitors. Although L2 is more susceptible to clavulanate than to tazobactam or sulbactam, there appears to be no correlation between the susceptibility to a  $\beta$ -lactamase inhibitor and the MIC of a  $\beta$ -lactam-inhibitor combination (341). Both L1 and L2 are chromosomally encoded and are inducible, and there is evidence that they share regulatory components (5, 364). Bonfiglio et al., however, recently described a clinical isolate of *S. maltophilia* with low-level expression of the L1  $\beta$ -lactamase which retained inducibility for the L2 enzyme (47). In addition, Payne et al. (329) reported another clinical isolate of the bacterium which elaborated high levels of carbapenemase without induction and suggested that this strain might have a mutation in its regulatory gene(s) which allowed the constitutive production of significant levels of enzyme.

The existence of additional  $\beta$ -lactamases produced by *S. maltophilia* was first suggested by Cullman and Dick (80), who described the presence of six distinct enzymes in 20 clinical strains of the bacterium. Subsequent reports have confirmed the heterogeneity of  $\beta$ -lactamase production in *S. maltophilia*, with the additional enzymes categorized as either serine enzymes or metalloenzymes (80, 326). Poor diffusion of penicillins and cephalosporins across the bacterial cell membrane has also been suggested as contributing to resistance to these compounds (79, 269), although it is unclear whether this arises from quantitative or qualitative differences in porin channels (79, 459). More recently, there have been instances of transferable cephalosporin and aztreonam resistance from nosocomial strains of *S. maltophilia* to recipient strains of *E. coli*, *Proteus mirabilis*, and *P. aeruginosa* (14, 188). Kelly et al. reported transferable penicillin and ceftazolin resistance in a clinical strain of *S. maltophilia* associated with a 5.6-kb plasmid (212). There have been no recorded instances of transferable carbapenem resistance.

Resistance to aminoglycosides mediated by aminoglycoside-

modifying enzymes is apparently uncommon in *S. maltophilia* (335). King et al. (225) described the production of aminoglycoside 6'-*N*-acetyltransferase by a single isolate of the bacterium. Vanhoof et al. (423), in their study of six clinical isolates, reported the expression of an aminoglycoside-*O*-nucleotidyltransferase and aminoglycoside 6'-*N*-acetyltransferase in one strain. Reduced uptake of aminoglycosides is possibly the most important mechanism which determines resistance to these compounds. Temperature-dependent aminoglycoside resistance was initially attributed to changes in outer membrane profiles (446).

More recent evidence from strains exhibiting both temperature-dependent and -independent resistance suggests that an altered cell surface microenvironment secondary to changes in the O side chains of lipopolysaccharides (347, 348, 423) is a more likely mechanism, with changes of the phosphate content of lipopolysaccharide at lower growth temperatures correlating well with decreased aminoglycoside susceptibility (349). Yu et al. reported the emergence of amikacin resistance in an isolate from a patient with infective endocarditis (467). Resistance was transferable to a strain of *P. aeruginosa*, but the mechanism of resistance was not investigated.

Resistance to quinolone agents is less well characterized. Resistant mutants are readily selected in vitro and are associated with qualitative and quantitative changes in outer membrane proteins (246). Cross-resistance to chloramphenicol and doxycycline in quinolone-resistant isolates has been reported by Lesco-Bornet et al. (246). The development of antimicrobial resistance in vivo has received comparatively little attention (69, 294). Manian et al. noted that 50% of 10 isolates lost susceptibility to at least one antibiotic during repeated isolations from intensive care unit patients (256). However, serial isolates were not subjected to a pheno- or genotypic typing technique, and the possibility of exogenous acquisition of a more resistant strain cannot be excluded. However, Garrison et al. used PFGE to demonstrate that resistant strains of *S. maltophilia* recovered from patients following therapy were indistinguishable from pretreatment isolates. In addition, they developed an in vitro pharmacodynamic chamber model, which permitted the observation of emergence of multiple resistance phenotypes during exposure to ceftazidime, ciprofloxacin, gentamicin, and ticarcillin-clavulanate (146).

Recently, Alonso and Martinez reported the presence of at least one multidrug resistance system in *S. maltophilia*, selected for by exposure to low concentrations of tetracycline. This energy-dependent efflux mechanism is effective against quinolones and chloramphenicol, as well as tetracyclines, but not against aminoglycosides or  $\beta$ -lactam drugs (6).

### Selection of Antimicrobial Agents

The selection of agents for use in the management of *S. maltophilia* infection presents a challenge to laboratorians and clinicians alike, not merely because of the aforementioned problems associated with susceptibility testing and the inherent resistance of the bacterium to many agents. While there is no shortage of in vitro studies of the activity of antimicrobial agents against *S. maltophilia*, there is a paucity of clinical investigations to determine the optimal therapy of infections associated with the bacterium; in particular, there have been no controlled trials, and recommendations for therapy are often based on retrospective studies and anecdotal reports.

Table 6 shows the susceptibility of *S. maltophilia* strains to selected antimicrobial agents. The wide range of values is, at least in part, explicable by differences in the susceptibility testing methods used by the investigators which, as noted above,

may significantly influence the observed results. Differing criteria for the definition of susceptibility and resistance and also the fact that some investigators have tested limited numbers of isolates also compound the difficulties in comparing studies.

There have also been very few studies which have examined the antimicrobial susceptibility of strains from disparate locations. Sader et al. tested isolates from the United States, Brazil, and Switzerland, although their results do not give a detailed comparison between country of origin and antimicrobial susceptibility (369). Despite their limitations, it is possible to draw general conclusions from the available data and to make broad recommendations for the therapy of *S. maltophilia* infection. With few exceptions (142, 427) most studies have found trimethoprim-sulfamethoxazole to be active against most strains of the bacterium, and this drug has long been regarded as the agent of choice for the therapy of *S. maltophilia* infection (113, 118, 178, 276, 355). This is despite the view that this drug is only bacteriostatic for most isolates, a fact which has prompted some authorities to recommend that this compound be used at close to the maximum tolerated doses (427). Toxicity of the sulfonamide component of the combination may prove to be a limitation of this approach (113). Resistance to trimethoprim-sulfamethoxazole has long been recognized (276). Although resistance to this drug may be increasing, Vartivarian et al. noted an increase in the trimethoprim-sulfamethoxazole susceptibility of isolates at the M. D. Anderson Cancer Center over a 12-year period. They attributed this to the discontinuation of this drug as a commonly used agent of antibacterial prophylaxis. Not unexpectedly, they observed a parallel increase in resistance to the quinolones—the compounds which replaced trimethoprim-sulfamethoxazole in this role—over the same period (427). Recently, Muder et al. suggested that a combination of trimethoprim-sulfamethoxazole and either ticarcillin-clavulanate or an extended-spectrum cephalosporin may be superior to trimethoprim-sulfamethoxazole alone (284).

There is near-universal agreement that the penicillins and cephalosporins, with a few exceptions, exhibit poor activity against *S. maltophilia*. The resistance of the bacterium to carbapenems, including newer members of this class (406) such as biapenem (367), is well recognized, although variations in the activity of these compounds have been noted. Piddock and Turner reported that three strains of *S. maltophilia* which were resistant to imipenem were susceptible to meropenem (336). Although several studies have shown that most strains tested are susceptible to the oxa- $\beta$ -lactam moxalactam (Table 6) (397), the hematologic side effects of this agent have precluded its continuing use in clinical practice. Of the extended-spectrum cephalosporins, ceftazidime appears to possess reasonable activity (144), although it must be stated that this is highly variable between strains, and this compound cannot be recommended for use as empirical therapy. Ticarcillin-clavulanate has been noted by several investigators to exhibit good activity against *S. maltophilia*, and it has been suggested that this agent should be used as the agent of choice in individuals intolerant of trimethoprim-sulfamethoxazole. In contrast, other  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations such as piperacillin-tazobactam (58, 122, 391), amoxicillin-clavulanate, and ampicillin-sulbactam (142) are poorly active against the bacterium. Only Fujita et al. have reported that 8 of 10 strains isolated from patients with *S. maltophilia* pneumonia were susceptible to a combination of cefoperazone and sulbactam (137).

Similarly, other combinations which have been evaluated, such as aztreonam-sulbactam, aztreonam-tazobactam (142), and clavulanic acid combined with carbenicillin, imipenem, ceftazidime, or aztreonam (142, 143), do not offer increased

TABLE 6. Susceptibility of *S. maltophilia* to selected antimicrobial agents

Antimicrobial agent	% Susceptibility	References
<b><math>\beta</math>-Lactam agents</b>		
Amoxicillin-clavulanate	0	142, 384
Aztreonam	0-7	124, 142, 197, 220, 241, 257
Ceftazidime	15-75	115, 137, 142, 178, 197, 220, 241, 249, 257, 300, 369, 384, 427, 462
Cefepime	30-57	249, 369, 462
Cefotaxime	2.5-63	124, 142, 218, 249, 296
Cefpirome	0-10	142, 300, 462
Cefsulodin	7-9	142, 241
Ceftriaxone	0-9	178, 220, 249, 462
Imipenem	0-4	115, 137, 142, 178, 218, 220, 241, 249, 257, 300, 365, 369, 384, 397, 427, 462
Meropenem	0-5	142, 249, 365
Moxalactam	43-100	115, 137, 142, 197, 218, 220
Piperacillin	0-89.3	115, 124, 137, 142, 197, 218, 220, 241, 249, 257, 462
Piperacillin-tazobactam	2-55	142, 241, 462
Ticarcillin	11.5-69	124, 142, 220, 241, 257, 296
Ticarcillin-clavulanate	25-96	220, 241, 300, 325, 384, 413, 427, 462
<b>Aminoglycosides</b>		
Amikacin	0-30	124, 137, 142, 178, 197, 220, 241, 257, 462
Gentamicin	0-63	11, 115, 124, 150, 178, 197, 257, 276, 277, 296, 390, 462
Streptomycin	10-44	145, 149, 150, 152, 276, 277, 390
Tobramycin	0-24	124, 137, 142, 197, 218, 241, 257, 390
<b>Tetracyclines</b>		
Doxycycline	81-91	142, 241
Minocycline	97-100	124, 137, 427
Tetracycline	2-69	145, 149, 150, 152, 178, 197, 276, 277, 330, 390
<b>Miscellaneous</b>		
Chloramphenicol	0-98	124, 145, 149, 152
Ciprofloxacin	0-100	11, 115, 141, 142, 178, 220, 221, 241, 249, 257, 384, 427, 462
Colistin	26-100	124, 145, 149, 220, 276, 277, 330, 390
Polymyxin B	35-100	149, 150, 152, 220, 276, 277
Rifampin	0-76	124, 220
TMP-SMX <sup>a</sup>	4-100	142, 178, 197, 220, 241, 257, 276, 279, 334, 384, 427, 462
Silver sulfadiazine	100	64

<sup>a</sup> TMP-SMX, trimethoprim-sulfamethoxazole.

activity against the bacterium with the exceptions of 2:1 and 1:1 (wt/wt) aztreonam-clavulanic acid (11, 143). However, the differing pharmacokinetics of these two agents dictate that levels of clavulanic acid in plasma decrease more rapidly than those of aztreonam, and the clinical applicability of this combination may be limited (143, 427). Rouse et al. reported synergy with a combination of cefoperazone and sulbactam in the treatment of *S. maltophilia* experimental pneumonia in mice (366), and Elkhaili et al. observed increased in vitro activity of a cefepime-clavulanic acid combination compared to the activities of the agents when used singly (113). It is unlikely that agents of the trimem (formerly tribactam) class of  $\beta$ -lactams

will have any useful role in the management of *S. maltophilia* infection (454).

Susceptibility to early examples of the quinolone class of antimicrobial agents, including ciprofloxacin (Table 6), varies markedly, but there have been anecdotal reports of response to these agents in systemic *S. maltophilia* infection (294, 457). However, both superinfection by *S. maltophilia* in patients receiving quinolones and therapeutic failures of *S. maltophilia* infection have been documented (69, 294), and the use of these compounds as empirical therapy must be considered with care. Newer quinolones, such as clinafloxacin, sparfloxacin, and trovafloxacin, appear to be more active against the bacterium than do the older agents in this class (23, 34, 62, 71, 88, 121, 131, 136, 182, 199, 221, 223, 224, 241, 251, 259, 315, 344-346, 350, 359-361, 368, 369, 391, 427). Pankuch et al., for example, reported that 93% of 25 ciprofloxacin-resistant strains were susceptible to clinafloxacin (315). Although these in vitro studies appear promising, there are at present few data on the use of the newer quinolones in the clinical setting, and the results of clinical studies are awaited with interest.

The activity of the aminoglycosides, including newer members of this class such as isepamicin (198, 221), against *S. maltophilia* is disappointing, and these agents, in general, play a very limited role as monotherapy. In vitro synergy has been observed when these agents have been used in combination with other antimicrobial agents (see below). The observation that liposomal preparations of some aminoglycosides are associated with decreased MICs compared with those of the free compound deserves further investigation (307).

Minocycline and doxycycline exhibit good in vitro activity against *S. maltophilia*, in marked contrast to tetracycline itself (Table 6) (300, 408), although clinical experience with these agents is extremely limited. Chloramphenicol has also been reported by several investigators (Table 6) as having good activity against the bacterium, and there are anecdotal reports of therapeutic success with this drug (20). The potential for hematologic side effects is of particular importance, and since many patients at risk of *S. maltophilia* infection have underlying disease-related or iatrogenic myelosuppression, chloramphenicol is not widely used in clinical practice. Because of the disappointing outcomes achieved with monotherapy in the management of *S. maltophilia* infection, it is not surprising that several investigators have proposed the use of combinations of antimicrobial agents, with much effort focusing on the identification of those two- or three-drug combinations which demonstrate in vitro synergy against the bacterium (30, 66, 72, 124, 156, 286, 299, 340, 362, 466).

It is difficult to draw firm conclusions from these studies, not only because of strain-to-strain variation and the wide variety of combinations tested but also because of the differing methods used. These include broth and agar dilution, checkerboard, and half-checkerboard techniques, as well as time-kill curves. Indeed, variations within studies have been observed in which combinations identified to be synergistic by the checkerboard method were found not to be so by killing-curve criteria (66, 124, 340). In addition, synergy may be strain dependent (88, 156). Furthermore, although combinations with demonstrable synergy in the laboratory setting have been associated with successful therapeutic outcomes, other combinations deemed to be nonsynergistic in vitro have also been associated with favorable clinical results (467). Moreover, it is important to note that although synergy between combinations of drugs may be demonstrable, synergy may not occur at clinically achievable concentrations (72). For example, in their investigation of the use of aerosolized amiloride in the therapy of *Pseudomonas* infections in cystic fibrosis patients, Cohn et al. were able to

TABLE 7. Combinations of antimicrobial agents showing in vitro synergy against *S. maltophilia*

Drug combination	Reference(s)
Sulfamethoxazole + colistin.....	299
Trimethoprim + colistin.....	299
Co-trimoxazole + carbenicillin.....	124
Co-trimoxazole + carbenicillin + rifampin.....	30, 466
Co-trimoxazole + ticarcillin-clavulanate.....	340
Co-trimoxazole + polymyxin B.....	286, 362
Ceftazidime + tobramycin.....	66
Cefepime-sulbactam + ciprofloxacin.....	114
Cefepime-sulbactam + amikacin.....	114
Ciprofloxacin + ceftazidime.....	72, 340
Ciprofloxacin + gentamicin.....	88, 155
Ciprofloxacin + mezlocillin.....	72
Ciprofloxacin + piperacillin-tazobactam.....	156
Ciprofloxacin + ticarcillin-clavulanate.....	340
Gentamicin + carbenicillin + rifampin.....	30, 466
Trovafoxacin + amikacin.....	434
Trovafoxacin + ceftazidime.....	434

demonstrate synergy between amiloride and tobramycin against three strains of *S. maltophilia* (74). However, this phenomenon was observed only at levels of amiloride in excess of those achievable in clinical practice. Studies in which synergy was demonstrated are summarized in Table 7.

Few data on the use of combinations of antimicrobial agents in clinical practice have been published, and they are derived from anecdotal evidence (168, 467) and noncontrolled studies (284), but the utility of these therapeutic approaches clearly deserves further study.

**Management of Infection by Means Other than Antimicrobial Agents**

In addition to antimicrobial chemotherapy in the management of *S. maltophilia* infection, several investigators have stressed the importance of removing infected vascular access devices (27, 115, 429) or prosthetic material (327, 415). Muder et al., however, reported the successful management of central venous catheter-related bacteremia without removal of the device (284).

**Prognosis**

Several investigators have examined factors which influence the outcome in *S. maltophilia* infection. In their prospective multicenter study of 91 cases of bacteremia, Muder et al. (284) found that hematologic malignancy, transplantation, neutropenia, immunosuppressive therapy, and a high severity of illness score (based on temperature, presence of hypotension, mental status, and the need for ventilatory support) were important. In contrast to other investigators (238), Muder et al. did not find a significant difference in acute mortality if *S. maltophilia* bacteremia was polymicrobial or monomicrobial in origin. They were unable to demonstrate a significant association between survival and administration of appropriate antimicrobial therapy (unlike another study [220]), although they acknowledged that the number of patients classified as being inappropriately treated may have been too small to allow meaningful statistical analysis.

**PREVENTION OF S. MALTOPHILIA INFECTION**

Several strategies to prevent *S. maltophilia* infection have been proposed. These include avoidance of inappropriate an-

tibiotic use and of prolonged implantation of foreign devices (118). Maintenance and, where appropriate, disinfection and/or sterilization of respiratory therapy equipment, cardiopulmonary bypass apparatus, hemodialyzers, and ice-making machines are also important (61, 129, 130, 274, 308, 342, 422, 433, 455). In addition, it may be prudent for neutropenic patients to avoid drinking noncarbonated bottled water, although carbonated water is acceptable (219).

During nosocomial epidemics of *S. maltophilia* colonization and/or infection, reinforcement of hand hygiene practices and wearing of gloves when handling contaminated respiratory secretions and wound drainage are of benefit (38, 172, 433). The cost-effectiveness of screening programs for *S. maltophilia* colonization in high-risk patients (175) requires further investigation before they can be recommended.

**CONCLUDING REMARKS**

Despite the recognition of *S. maltophilia* as a significant human pathogen, primarily in the nosocomial but also in the community setting, comparatively little is known about the bacterium, particularly with regard to putative virulence factors. With continuing advances in medical technology, including treatment regimens which are associated with iatrogenic immunosuppression, and the growth of at-risk populations, such as those with AIDS, the incidence of infection associated with *S. maltophilia* will almost certainly increase. Management of these infections presents problems for both the laboratorian and clinician. In particular, methods for determining the susceptibility of *S. maltophilia* to antimicrobial agents, which are at present often unreliable, require further development. The role of alternative therapeutic agents in the management of *S. maltophilia* infection, particularly the newer quinolones, deserves continued examination. Similarly, there is a need to evaluate in the clinical setting the utility of antimicrobial combinations which have been shown to exhibit in vitro synergy against the bacterium. Much remains to be understood of the epidemiology of *S. maltophilia*, although the development of rapid, inexpensive, and reproducible typing systems, coupled with the availability of selective culture media, will permit systematic investigation of this topic. In particular, more information on nosocomial reservoirs and routes of transmission of the bacterium is needed; this is essential for the development of effective infection control strategies. It is likely, however, that *S. maltophilia* will present a major challenge to microbiologists, clinicians, and hospital epidemiologists for some time to come.

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