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Antibiotic Treatment of Multidrug-Resistant Organisms in Cystic Fibrosis

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Abstract

Respiratory tract infection with eventual respiratory failure is the major cause of morbidity and mortality in cystic fibrosis (CF). Infective exacerbations need to be treated promptly and effectively to minimize potentially accelerated attrition of lung function. The choice of antibiotic depends on *in vitro* sensitivity patterns. However, physicians treating patients with CF are increasingly faced with infection with multidrug-resistant isolates of *Pseudomonas aeruginosa*. In addition, innately resistant organisms such as *Burkholderia cepacia* complex,

Stenotrophomonas maltophilia and *Achromobacter (Alcaligenes) xylosoxidans* are becoming more prevalent. Infection with methicillin-resistant *Staphylococcus aureus* (MRSA) is also a problem. These changing patterns probably result from greater patient longevity and increased antibiotic use for acute exacerbations and maintenance care.

Multidrug-resistant *P. aeruginosa* infection may be treated successfully by using two antibiotics with different mechanisms of action. In practice antibiotic choices have usually been made on a best-guess basis, but recent research suggests that more directed therapy can be achieved through the application of multiple-combination bactericidal testing (MCBT). Aerosol delivery of tobramycin for inhalation solution achieves high endobronchial concentrations that may overcome bacterial resistance as defined by standard laboratory protocols. Resistance to colistin is rare and this antibiotic should be seen as a valuable second-line drug to be reserved for multidrug-resistant *P. aeruginosa*. The efficacy of new antibiotic groups such as the macrolides needs to be evaluated.

CF units should adopt strict segregation policies to interrupt person-to-person spread of *B. cepacia* complex. Treatment of panresistant strains is difficult and often arbitrary. Combination antibiotic therapy is recommended, usually tobramycin and high-dose meropenem and/or ceftazidime, but the choice of treatment regimen should always be guided by the clinical response.

The clinical significance of *S. maltophilia*, *A. xylosoxidans* and MRSA infection in CF lung disease remains uncertain. If patients show clinical decline and are chronically colonized/infected with either of the former two pathogens, treatment is recommended but efficacy data are lacking. There are defined microbiological reasons for attempting eradication of MRSA but there are no proven deleterious effects of this infection on lung function in patients with CF. Various treatment protocols exist but none has been subject to a randomized, controlled trial.

Multidrug-resistant microorganisms are an important and growing issue in the care of patients with CF. Each patient infected with such strains should be assessed individually and antibiotic treatment planned according to *in vitro* sensitivity, patient drug tolerance, and results of *in vitro* studies which may direct the physician to antibiotic combinations most likely to succeed.

About 1 in 25 Caucasians are heterozygote carriers of a mutant cystic fibrosis transmembrane regulator (CFTR) gene, making cystic fibrosis (CF) the most common inherited genetic illness in this population. CF is also found, although less frequently, in most other ethnic groups.[1] Although it is a multisystem disease, morbidity and mortality closely parallel respiratory tract dysfunction.[2] Respiratory infection is almost inevitable. Traditionally, children with CF were thought to be infected first with *Staphylococcus aureus*, later with *Pseudomonas aeruginosa*, and intermittently with *Haemophilus influenzae*. We now know that infection with these or other microorganisms may occur in infancy and become established by early childhood.[3,4] In the US, 30% of 2- to 5-year-olds with CF and 81% of 26- to 30-year-olds with CF are infected with *P. aeruginosa*. Infections with *P. aeruginosa*, almost always, and with *S. aureus* often, are impossible to eradicate once they have become chronic. Nonetheless, respiratory function improves with antibiotic therapy[5] and many CF centers in Europe follow the Copenhagen protocol which recommends 3-monthly courses of intravenous antibiotic for chronic *P. aeruginosa* infection irrespective of the patient's clinical condition.[6]

As median life expectancy for patients with CF has increased to their early 30s,[2] we are faced with a population that has received multiple intravenous and oral antibiotic treatments. Repeated exposure to antibiotics has encouraged the development of bacterial resistance in *P. aeruginosa* and may be associated with the emergence of intrinsically resistant organisms such as *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*. Repeated hospital admissions increase the risk of acquiring methicillin-resistant *S. aureus* (MRSA). Clinicians are increasingly faced with the dilemma of how best to treat patients who harbor these multidrug-resistant organisms. In this article we discuss a practical approach to the problem.

1. *Pseudomonas aeruginosa*

1.1 Background

P. aeruginosa is the microorganism most frequently isolated from CF sputa; this bacterium infects 59% of CF patients in the US.[2] This opportunistic pathogen's ability to persist in the CF lung involves an unusual bacterial adaptation including phenotypic change, alginate biosynthesis and mucoidy.[7] Most physicians treat *P. aeruginosa* respiratory exacerbations with two appropriate antibiotics as determined by *in vitro* susceptibility tests. Combination therapy significantly reduces bacterial density and is associated with longer clinical remission.[5,6,8] In the UK, in non-CF patients, antibiotic resistance to *P. aeruginosa* remains low at less

than 12%,[9] but higher levels of resistance have been reported from patients with CF both in the UK and in Canada.[9,10] Moreover, many *P. aeruginosa* isolates have become multidrug-resistant, defined as strains resistant to all antibiotics in two of the three following classes consisting of aminoglycosides, β-lactam agents including the carbapenems and the monobactam aztreonam, or fluoroquinolones.[11] This is probably a consequence of constant antibiotic selective pressure.[12] Interestingly, up to 49% of isolates reported as resistant or of intermediate sensitivity have been found to be susceptible on central retesting.[9]

It can be difficult to define what is meant by 'susceptible' and 'resistant' and to draw international comparisons. Many countries have their own systems for defining susceptibility and resistance and may give differing views on the appropriate methods to determine these. In the US this is the responsibility of the National Committee for Clinical Laboratory Standards (NCCLS) and in the UK it is the British Society for Antimicrobial Chemotherapy (BSAC). However, it is important that each country should have facilities in place to provide the reference services needed to identify multidrug-resistant strains, determine their mechanisms of resistance and provide advice about appropriate treatment. Whether such services are specific for CF units or form part of a national provision for all patients will depend on available resources and clinical need. However, units with small numbers of patients with CF and where laboratory staff may have little experience with multidrug-resistant *P. aeruginosa* infection should consider sending such samples to a nationally recognized reference center.

1.2 Choosing the Appropriate Antibiotic

Although it is recommended that antibiotics are chosen according to bacterial resistance patterns,[13] it is difficult to correlate *in vitro* sensitivity patterns with *in vivo* efficacy in the treatment of CF respiratory exacerbations. Antibiotic concentrations tested *in vitro* may relate poorly to endobronchial drug levels. In addition, patients are likely to have infection with multiple phenotypes of *P. aeruginosa* with differing antibiotic susceptibilities. When outcome measures were compared, no differences were found between patients treated with antibiotics to which their *P. aeruginosa* isolates were sensitive and those treated with antibiotics to which the isolates were resistant.[14]

Bactericidal antibiotic concentrations cannot reliably be achieved in CF sputum through the intravenous route. Peak sputum levels may reach only 12% of the serum drug concentration, and one *in vitro* study suggested that tobramycin levels 25 times the minimum inhibitory concentration may be needed for bactericidal effect.[15] However, suboptimal antibiotic concentrations can promote clinical improvement by inactivating oxygen radicals and inhibiting pseudomonal virulence factors[16-18] such as exotoxin A, total protease, elastase, phospholipase C, lipase and lecithinase. Although the drug combination should include one antibiotic to which the bacteria are sensitive when this is possible, even panresistant organisms should always be treated with antipseudomonal antibiotics. In the latter situation, antibiotic combinations should be chosen based on the patient's previous clinical response.[13]

1.3 Combination Therapy

Combinations of antibiotics may have *in vivo* synergy and should be used both to prevent the development of resistance[19,20] and to treat multidrug-resistant *P. aeruginosa*. Saiman et al.[21] showed that 75% of highly resistant *P. aeruginosa* strains could be inhibited by clinically achievable levels of one or more antibiotic pairs with on average 3 additive and 2.4 synergistic combinations per strain. Weiss and Lapionte[22] showed synergy in 19–39% of 122 isolates of *P. aeruginosa* when tobramycin was combined with either ticarcillin, piperacillin, ceftazidime or imipenem. It seems logical to enhance any potential additive effect by combining antibiotics that have different mechanisms of action, e.g. aminoglycosides inhibit bacterial protein synthesis, quinolones inhibit DNA synthesis, β-lactam agents inhibit bacterial cell wall biosynthesis and colistin interacts with cell membrane phospholipids. The choice of combination antibiotic therapy is usually made empirically on these grounds and on the patient's past clinical responses to treatment. However, it is not known whether such combination regimens are the optimal choice for individual patients.

At times, an educated guess can go wrong. Lang et al.[23] showed that in 29% of isolates that were sensitive to a single antibiotic, bactericidal activity was lost when a second empirically chosen antibiotic was added. Such a high incidence of antagonistic combinations is not universal. Saiman et al.[21] found only a 3% incidence in 172 highly resistant strains, and Weiss and Lapionte[22] found no antagonism in a more limited study of four antibiotic combinations which included tobramycin in each of the combinations.

Lang et al.[23] argued that traditional methods testing only susceptibility to single antibiotics are of limited value with multidrug-resistant *P. aeruginosa*. They developed a multiple-combination bactericidal test (MCBT). This systematically tests isolates against different combinations of antibiotics to determine optimal sensitivity patterns. Results are available within 72 hours of culture of the *P. aeruginosa* isolate from the sputum and logical antibiotic choices can be made early in the treatment course. If isolates were tested at routine clinic visits this information would be available at the beginning of any respiratory exacerbation. The most effective single antibiotic was meropenem, bactericidal against 44% of *P. aeruginosa* isolates. The most effective intravenous combination was meropenem with ciprofloxacin which was bactericidal against 85% of the isolates. This may reflect the fact

that meropenem is a relatively new drug and widespread resistance has not yet emerged.

Tobramycin was the second most effective single antibiotic and meropenem/tobramycin the next most effective combination. Shawar et al.[24] also found that tobramycin had good activity against multiresistant strains of *P. aeruginosa* and that only 5% of all strains were tobramycin resistant. Up to 84% of isolates resistant to β-lactam agents and/or ciprofloxacin were susceptible to tobramycin. Saiman et al.[21] reported that antibiotic combinations including tobramycin were the most active.

Most CF clinicians do not have access to MCBT and should consider including meropenem or tobramycin in their empirical choice of antibiotic combinations. Lang et al.[23] concluded that further controlled trials were needed to fully evaluate the usefulness of MCBT in CF care. These early studies suggest that it has significant potential for optimizing antibiotic treatment against multidrug-resistant *P. aeruginosa* isolates.

1.4 Other Antibiotic Treatments

The efficacy of antibiotics against *P. aeruginosa* may be increased by maximizing antibiotic delivery, e.g. once-daily administration of aminoglycoside,[25] continuous intravenous delivery of ceftazidime[26] or combining intravenous and nebulized delivery of antibiotics. Lang et al.[23] showed that a high concentration of tobramycin (200 μg/mL) was bactericidal against 72% of the isolates and achieved 88–94% bacterial kill rates *in vitro* when combined with another antipseudomonal antibiotic. It is not possible to reach this concentration *in vivo* with intravenous delivery of tobramycin but sputum concentrations above this level can be realized with aerosolization of tobramycin for inhalation solution (TOBI). The authors suggest that the best combination against multidrug-resistant *P. aeruginosa* strains is inhaled TOBI plus a second intravenous antibiotic such as mecropenem, tazocin or ciprofloxacin. Each isolate was sensitive to one or more dual-antibiotic combinations, which included high-dose tobramycin. Similarly, Saiman et al.,[21] in a study of antibiotic activity against *P. aeruginosa* isolates from patients not responding to conventional antibiotic regimens, found that 95% of the strains were inhibited by high levels of tobramycin (100–200 μg/mL) achieved via aerosol administration.

Isolates of *P. aeruginosa* have shown very little resistance to colistin,[27] which acts by penetration of the bacterial cell envelope. This causes irreversible damage to the cytoplasmic membrane. The resistance mechanisms used by *P. aeruginosa* against antibiotics with specific cellular enzyme targets cannot be used against colistin. Nor does *P. aeruginosa* appear capable of modifying the lipopolysaccharide binding site by which colistin gains entry to cells. Nonetheless, the UK is the only European country where colistin is administered intravenously because of historical, though largely unfounded concerns related to potential toxicity.[28,29] Colistin is rarely used in the US and is only just beginning to be introduced in Australia (Coulthard K, personal communication). We have successfully used colistin in both pediatric and adult patients with CF over the last 10 years without any serious adverse events and with good clinical efficacy. We recommend that the use of intravenous colistin is reserved for resistant *P. aeruginosa*.

The role of macrolide antibiotics in the treatment of multidrug-resistant *P. aeruginosa* warrants study.[30] *In vitro* work has shown an inhibitory activity on the production of alginate and other pseudomonas virulence factors.[31] A recent randomized, controlled, double-blind study of azithromycin 250mg (body weight ≤40kg) or 500mg (body weight >40kg) once daily use in children showed a significant improvement in respiratory function in the active treatment arm.[32] The anti-inflammatory effects may benefit patients with multidrug-resistant infection.

1.5 Preventing the Spread of Multidrug-Resistant Isolates

Epidemiological studies of *P. aeruginosa* transmission in hospitalized patients with CF have produced conflicting results. Many have found little evidence of patient-to-patient transmission.[33-36] However, ceftazidime monotherapy has been associated with major outbreaks of multidrug-resistant *P. aeruginosa* in two large European CF centers.[19,37]

It is therefore recommended that two antibiotics are routinely prescribed for the treatment of sensitive *P. aeruginosa* infection in patients with CF, usually a combination of an aminoglycoside and a β-lactam agent.

Recent reports[38,39] have highlighted the possibility of within-center spread of transmissible, highly resistant strains of *P. aeruginosa*. Our own Pediatric CF Unit has recently experienced inpatient transmission of an unusual colistin-resistant strain of *P. aeruginosa*.[40] Regular epidemiological surveillance is needed to evaluate the strains present within any clinic population, although the method of choice, pulsed-field gel electrophoresis, is time consuming and expensive. Ideally, patients with multidrug-resistant strains of *P. aeruginosa* should be kept in isolation.

2. *Burkholderia cepacia* Complex

2.1 Background

In the UK the incidence and prevalence of *B. cepacia* complex within the CF community has increased dramatically over the past 20 years, with the organism emerging as an important respiratory pathogen. This has resulted from improved microbiological isolation techniques in conjunction with the emergence of a highly transmissible epidemic strain at a time when there was an absence of effective patient segregation in many CF units.[41,42] Epidemics have occurred following patient-to-patient contact in both the hospital and social environment.[41-43] As a result, strict segrega-

tion policies are now routine and greater emphasis has been placed on the importance of microbiological surveillance and the standardization of both culture media and laboratory protocols. Reference laboratories have been set up across the US, Canada and Europe to provide assistance in identification of putative *B. cepacia* species.

2.2 Taxonomy

The taxonomy of *B. cepacia* has continued to expand and there are now nine types, known as genomovars (gv), that have been identified.[44,45] The majority of isolates from CF sputum are from the gv III and *B. multivorans* groups.[45-47] So called epidemic strains, such as the cable pilus encoding strain ET12 (which caused massive epidemics across Canada and Europe) usually belong to gv III.[41,42,48] Furthermore, specific DNA markers, such as the *B. cepacia* epidemic strain marker (BCESM) and the cable pili subunit gene (cblA), have also been identified within specific epidemic strains. BCESM appears to be the more robust marker of transmissibility but may be absent from epidemic strains.[43,46-48]

2.3 Clinical Outcome

Although the clinician is faced with an increasingly complex nomenclature for *B. cepacia* complex, it is important to remember that genomovar classification alone cannot predict clinical outcome in any individual patient. Some patients infected with the same genomovar of *B. cepacia* complex may remain clinically stable, whereas others may experience a decline in lung function. Up to a third of patients develop a rapidly fatal necrotizing pneumonitis, which can be accompanied by systemic sepsis and bacteremia.[48-50] This fulminating form of *B. cepacia* complex infection is often referred to as the cepacia syndrome and is usually associated with gv III strains.[51] *B. cepacia* complex is also associated with excess early mortality in patients after lung transplant, and again it is the gv III strains that appear to carry a particularly poor postoperative prognosis.[52-55] Many transplant centers now consider infection with *B. cepacia* complex a contraindication to transplant.

Autopsy studies (in lung explants) suggest that *B. cepacia* complex is principally distributed in the peripheral rather than proximal airways.[56] During acute infection some strains appear to invade injured airway surfaces and can even migrate into the lumen of blood capillaries. The pathogenicity of *B. cepacia* complex may be due in part to an innate ability to resist non-oxidative neutrophil-mediated killing and the ability of the organism to survive intracellularly within phagocytes.[57]

2.4 Segregation Policies

The clinical course of infection with *B. cepacia* complex varies according to genomovar status, with gv III being associated with a poorer clinical outcome.[45] Many centers now advocate subsegregation within the *B. cepacia* complex group in an attempt to reduce the risk of further cross-infection. Recent studies have shown that *B. multivorans* can be replaced by transmissible gv III strains.[58]

We recommend that all patients infected with *B. cepacia* complex are segregated from one another as well as from all other patients with CF. This can be achieved in outpatients by having more than one waiting area and by introducing gaps of 10–15 minutes between patient appointments. All inpatients should be nursed in individual cubicles. The *B. cepacia* complex ward should not have a communal patient room. To minimize the negative effects of isolation, all patient rooms should have television, video recorder, fridge and telephone access. Ward staff must make special efforts to spend time with each patient.

Transient *B. cepacia* complex colonization, although infrequent, does occur. In these cases our approach is to discontinue formal segregation of patients after a year of repeated negative sputum microbiology. In time, segregation is likely to result in a progressive increase in the proportion of patients acquiring unique environmental strains, which it is hoped will remain less virulent.

2.5 Antibiotic Therapy

B. cepacia complex isolates are inherently resistant to colistin. Resistance to other antibiotics is variable and is conferred by a number of different mechanisms including β-lactamase production, altered penicillin-binding proteins, reduced permeability and antibiotic efflux pumps. The choice of antibiotics for the treatment of panresistant strains of *B. cepacia* complex is often arbitrary and difficult. Combinations of two or three antibiotics are usually used. A proportion of patients will have concomitant *P. aeruginosa* infection and therapy is then usually guided by antibiotic sensitivity to this organism. In this group of patients prophylactic nebulized antibiotic therapy with TOBI or colomycin could be continued in an attempt to reduce exacerbation rates. For patients infected solely with *B. cepacia* complex, a combination of tobramycin 10 mg/kg once daily with high-dose meropenem 40 mg/kg 3 times daily (maximum dose and adults 2g three times daily) and/or ceftazidime 100 mg/kg twice daily (maximum dose 6g twice daily) is recommended, as this combination appears to confer effective *in vitro* bactericidal activity.[59-61] Where the sputum shows intermediate or full sensitivity to ciprofloxacin, the use of this agent in combination with meropenem or piperacillin 90 mg/kg three or four times per day (>12 years 4.5g three or four times per day up to a maximum dose of 4.5g four times daily) may increase bactericidal activity.[62]

The antibiotic regimen should always be guided by clinical response and combinations altered where and when appropriate. Other agents such as chloramphenicol, trimethoprim/sulfamethoxazole (cotrimoxazole), rifampin (rifampicin) and minocycline have some activity against *B. cepacia in vitro*, although

their clinical effectiveness remains unclear.[61,63,64] Current *in vitro* susceptibility tests offer clinicians a rationale for selecting antibiotic regimens but there is frequently a discrepancy between laboratory results and clinical outcome. As a result, there is now a growing interest in the potential usefulness of *in vitro* synergy testing of *B. cepacia* isolates but such tests are not widely available. Studies suggest that although multiple combination therapy may provide highly effective bactericidal activity *in vitro*, it may be associated with reduced efficacy *in vivo* because of antibiotic antagonism.[59]

2.6 Outcome

Most patients improve with conventional therapy, whereas others respond transiently but have subsequent frequent exacerbations and persistently elevated inflammatory markers.[65] In the latter case, patients can sometimes be stabilized by the introduction of routine frequent, or continuous, intravenous antibiotic therapy with ceftazidime, meroprenem, aztreonam, tobramycin or tazocin.

Patients with *B. cepacia* complex infection have an increasing prevalence of chronic nausea and anorexia and more frequently require nutritional support. Early intervention with nasogastric or gastrostomy feeding can help maintain nutritional status.[66]

2.7 The Patient's Perspective

Informing patients for the first time that they have *B. cepacia* complex infection is extremely difficult because it has many implications for the individual concerned. Not surprisingly, many patients are frightened by the prospect of infection with this organism, whose potential effects are well known within the CF community. The isolation of *B. cepacia* complex is also synonymous with a significant change in lifestyle, with loss of contact with fellow patients and transfer into an environment of segregation and isolation. Psychological support should be available where appropriate.

3. *Stenotrophomonas maltophilia*

3.1 Background

S. maltophilia is a multidrug-resistant Gram-negative bacillus isolated with increasing frequency from the respiratory tract of patients with CF. It was first identified in 1943, when it was named *Bacterium bookeri*.[67] After a number of taxonomic studies it was designated *Pseudomonas maltophilia* in 1961, reclassified as *Xanthomonas maltophilia* in 1983 and finally placed in a new genus, *Stenotrophomonas*, in 1993. It is also an important nosocomial pathogen for patients without CF, particularly those who are immunocompromised following chemotherapy for hematological malignancies.[67]

3.2 Epidemiology

S. maltophilia was first isolated from the sputum of patients with CF during the 1970s.[68,69] Its prevalence has increased steadily, with reports ranging from about 15–30%[70-73] in some European CF centers and 5–10%[74,75] in the US. There is no clear correlation between age and acquisition[71,76] but prior use of antibiotics and admission to hospital have been identified as risk factors for patients with CF.[71,77] The epidemiology of *S. maltophilia* in CF remains unclear. Several genotyping studies have found little evidence of patient-to-patient transmission of the organism in CF centers.[76,78,79] This is consistent with the findings of studies in non-CF patients.[67] The organism is widely disseminated in both the home and hospital environments of patients[78] and is found mainly in association with water and plumbing systems (e.g. portable water, faucets, sink drains, etc.). It has also been found to contaminate equipment used to deliver aerosolized antibiotics.[80,81] This may relate to the practice of rinsing reusable nebulizer equipment in faucet water. In one study, patients paying close attention to thorough drying of equipment after washing had the lowest contamination rates.[80]

3.3 Clinical Significance

The clinical significance of *S. maltophilia* is the subject of much controversy. *S. maltophilia* has been shown to adhere to and invade human epithelial respiratory cells *in vitro*.[82] However, the potential of *S. maltophilia* lipopolysaccharides to induce inflammatory responses in human monocyte cell lines is significantly less than that of *P. aeruginosa* or *B. cepacia*.[83,84] To date, there has not been a comprehensive controlled study analyzing the clinical significance of *S. maltophilia* colonization in patients with CF. The majority of patients appear to experience only transient colonization[74,75] with no evidence of clinical deterioration. However, some patients are chronically colonized, with bacterial counts of $>10^5$ colony-forming units/mL[73,85] for several months or more,[72,76] and this has been associated with gradual deterioration in their clinical condition. To date there have been no reports of any rapid clinical decline as seen with some patients infected with gv III strains of *B. cepacia* complex.

3.4 Antibiotic Resistance and Treatment Choices

S. maltophilia is resistant to most of the commonly used antipseudomonal antibiotics, including carbapenems. A combination of β-lactamases, reduced permeability and the existence of efflux pumps mediates this resistance.[67] The results of *in vitro* susceptibility tests can also be unreliable, with many strains reported as falsely susceptible.[86] Studies examining the clinical efficacy of different agents in the treatment of significant infections with *S. maltophilia* are lacking, and data are extrapolated mainly from *in vitro* studies.

Trimethoprim/sulfamethoxazole has consistently been shown to be the most active agent *in vitro*, with most isolates susceptible on initial testing.[67,87] This is regarded as the treatment of choice for significant infections with *S. maltophilia*. Some antipseudomonal agents, such as ceftazidime, ticarcillin/clavulanic acid, ciprofloxacin and colistin, have been shown to have moderate activity against some strains of the organism.[67,87] Because the activity of trimethoprim/sulfamethoxazole (adult dosage 960mg twice daily) is only bacteriostatic, it has often been tried in combination with other agents such as ticarcillin/clavulanic acid or ceftazidime[87] when treating significant infections in immunocompromised patients. There are no data available regarding the efficacy of trimethoprim/sulfamethoxazole, alone or in combination, for the treatment of chronic *S. maltophilia* colonization in patients with CF.

Another agent with potential for treating *S. maltophilia* infections is minocycline. The majority of strains from patients in one study were found to be susceptible.[63] Again, no data exist regarding clinical efficacy, although minocycline 100mg twice daily has been used to successfully treat *S. maltophilia* pneumonia in a patient with bronchiectasis.[88] New therapeutic developments include antimicrobial peptides but their *in vitro* activity has been relatively modest against CF strains of *S. maltophilia* thus far.[89,90]

3.5 Infection Control

Many units have considered segregating patients who are colonized with *S. maltophilia* because of concerns over controlling the spread of a multiresistant organisms. However, the lack of evidence for patient-to-patient transmission suggests that this is largely unhelpful. The widespread distribution of *S. maltophilia* in the environment of CF patients suggests that infection control efforts should be focused on reducing risks associated with these sources.

4. Methicillin-Resistant *Staphylococcus aureus*

4.1 Background

S. aureus was the predominant respiratory pathogen in patients with CF until the 1950s. MRSA was first identified in the 1960s soon after the introduction of methicillin (an early precursor of flucloxacillin).[91] Its prevalence in the community varies widely but appears to be increasing. By 1969, in Denmark, MRSA was identified in 20% of blood cultures containing *S. aureus*.[92] In the US in 1986, 2.4% of all *S. aureus* isolates were methicillin resistant. By 1991 this figure had risen to 29%.[93] In Dublin, in the first quarter of 1993, 47% of all *S. aureus* isolates were methicillin resistant.[94] The Wales surveillance unit reported a 5.2 per 100 000 incidence of MRSA from bacteremias and cerebrospinal fluid compared with 12.7 per 100 000 for methicillin-sensitive *S. aureus*.[95]

4.2 Prevalence

The prevalence of MRSA in the CF population is likely to reflect that in the local community. Givney et al.[96] showed that nosocomial transmission from other hospital patients was common, but only one instance of possible transmission between two patients with CF was identified. In 1998 in Lewisham, UK, 13 (17%) patients with CF were found to be colonized with MRSA. Eight patients had the same strain (named by the UK Public Health Laboratory Service as epidemic methicillin-resistant *Staphylococcus aureus* type 16 or EMRSA-16) which was prevalent in other patient populations in that hospital at the time.[97] The Royal Brompton Hospital in London, UK reported a low but increasing prevalence of MRSA infection in patients with CF. Between 1965 and 1998, 2.7% of patients with CF were infected with MRSA.[98] Boxerbaum and colleagues[99] reported 3% of children with CF who had MRSA infection. Miall et al.[100] have reported a similar figure in a pediatric population; they also demonstrated an increasing trend of MRSA infection in CF patients with no cases reported in 1992 and seven cases in1994.

4.3 Clinical Consequences of Infection

The pathogenicity of different strains of MRSA appear to vary. Some strains, e.g. EMRSA-16, are associated with a higher incidence of chest infection and death compared with infection with methicillin-sensitive organisms.[101] Several studies have suggested an increase in mortality in non-CF patients infected with MRSA.[102,103]

Although the pathogenicity of MRSA is considered to be equivalent to that of methicillin-sensitive *S. aureus*,[104] its effects on morbidity and mortality in CF are still debated. Several small, short-duration and uncontrolled studies have suggested a minimal effect.[96-99] A recent uncontrolled study in children with CF, reporting a 6.5% incidence of infection with MRSA, demonstrated no clinical impact.[105] Miall et al. examined the effect of MRSA on various clinical parameters over a 12-month period and found that CF children with MRSA infection showed a significant worsening of height standard deviation scores and required twice as many courses of intravenous antibiotics compared with controls.[100]

Another clinical consequence of MRSA infection in CF patients is the potential negative effect on future lung transplant. Most transplant centers reject MRSA-positive patients. Many CF centers use a policy of separate clinic visits for MRSA-colonized patients, and discourage social contact. Patients thus face the added problem of social isolation.

4.4 Management of MRSA-Colonized/Infected Patients

Some CF centers use flucloxacillin as prophylaxis against *S. aureus* infection. Although there has been concern that this may

contribute to the development of resistance by selection of mutant MRSA strains, it is generally believed that this is unlikely. The emergence of MRSA infection in CF patients appear to be occurring at the same rate and time as the epidemic in non-CF patients.[97]

Treatment should be aimed at prevention. Asensio et al.,[106] showed six independent risk factors for MRSA infection/colonization in patients without CF. These risk factors were age (every 10 years of age, odds ratio [OR] = 1.3), type of ward (surgical, OR = 1; medical, OR = 3.1; intensive care unit, OR = 60), previous hospitalization (OR = 6.9), coma (OR = 25.3), invasive procedures (each, OR = 1.7), and ≥3 weeks of hospitalization (OR = 3.8). They did not show that antibiotic therapy was a risk factor on its own.

These results offer a basis for reduction of MRSA infection/colonization in hospital for all patient categories including early identification of infection or colonization, patient segregation, reduction of hospital admissions to a minimum and meticulous attention to hygiene, such as hand-washing by all staff and contacts, especially with invasive procedures.[107] Frequent sputum culture is essential for early identification of patients with CF who are colonized with MRSA. Patient segregation is necessary although it is important to avoid stigmatization and isolation. An equipment policy should be developed with the assistance of the local infection control team. Some units implement strict barrier nursing protocols. Others have suggested screening family members of patients colonized with MRSA because some of them may also be colonized and be potential sources for future reinfection.[108]

We are not aware of any published randomized, controlled trials examining eradication protocols for patients with CF and MRSA. It is therefore necessary to apply techniques and experience gained from other patient groups. Most of the literature discusses eradication of MRSA from the nose and pharynx. Patients with CF present the additional challenge of eradication of the bacteria from the lower airway and possibly the gastrointestinal tract. The most common sites colonized in patients with CF are the lower airway (96%), nose (23%), skin (15%)[98] or oropharynx.[99] Rectal carriage can occur in more than 70% of patients who swallow infected sputum.[109,110] MRSA colonization of patients with CF is probably transient in 35% of cases.[98]

4.4.1 Nasal and Skin Colonization

Regimens aimed at eradicating MRSA from the nasopharynx and skin usually involve nasal mupirocin (a naturally occurring antibiotic produced by submerged fermentation of *Pseudomonas fluorescens*) and chlorhexidine baths or showers. They are effective in up to 75% of non-CF patients.[111,112] The usual recommended dosage is mupirocin 0.5g inserted into each nostril twice daily for 5–10 days.[113] This has been demonstrated to be effective even with mupirocin-resistant strains of MRSA.[114] An alternative regimen with equal efficacy is topical fusidic acid and oral trimethoprim/sulfamethoxazole.[115]

Other infection control measures include application of chlorhexidine acetate 1% powder to axilla and groin areas, chlorhexidine gluconate 1% mouth wash four times a day and a daily antiseptic body wash with triclosan 2%, povidone iodine 4% or chlorhexidine gluconate 4%.

4.4.2 Gut Colonization

American guidelines do not recommend the use of oral vancomycin to reduce gut colonization with MRSA. There is concern that it will encourage the emergence of vancomycin-resistant enterococci or vancomycin-resistant *S. aureus*.[116]

4.4.3 Lower Respiratory Tract Colonization

It is important to choose antibiotic regimens guided by MRSA culture sensitivity information. This can vary widely with time and region.[117,118] MRSA strains commonly demonstrate *in vitro* sensitivity to a number of antibiotics, including vancomycin, teicoplanin, fusidic acid, trimethoprin/sulfamethoxazole, tetracyclines, rifampin, dalfopristin-quinupristin, linezolid and, occasionally, macrolides. Most regimens used by CF centres in the UK use a combination of the above antibiotics administered systemically and/or as nebulized therapy.

Vancomycin 1g twice daily is the antibiotic most commonly used against MRSA and is given intravenously.[119,120] It may be associated with significant adverse effects and interactions.[121] Teicoplanin can be used as an alternative. Rifampin in combination with vancomycin has been shown to be effective in treating MRSA infections in patients with severe burns that are unresponsive to vancomycin alone.[122]

Eradication practices for lower respiratory tract infection with *P. aeruginosa* in patients with CF have demonstrated that combined nebulized and systemic treatments are most effective.[123] Many CF units use nebulized vancomycin 5 mg/kg 3–4 times per day made up to 4ml with saline with pretreatment with inhaled albuterol (salbutamol) in MRSA eradication regimens.[105]

Fusidic acid and rifampin should not be used as single agents, as resistance rapidly develops.[124] Oral fusidic acid used as a single agent fails to eradicate MRSA and results in the rapid emergence of resistant strains.[125] There is evidence that various combinations may be effective in non-CF patients, including trimethoprim/sulfamethoxazole and rifampin for skin and nose MRSA colonization,[126] fusidic acid and rifampin,[127] minocycline and rifampin and nasal mupirocin.[128]

Oxazolidinones are a new class of antibacterial agents that have a unique mechanism of action involving inhibition of the initiation step of protein synthesis. They do not induce cross-resistance to other classes of antibiotics. The first marketed member of the class, linezolid, shows good efficacy against MRSA and has near-complete oral bioavailability plus favorable pharmacokinetic and

adverse-effect profiles.[129] *In vitro* activity is similar to that of vancomycin.[130] The drug is approved for skin infections and nosocomial pneumonia caused by MRSA.[131] It is not licensed for use in children.

Quinupristin/dalfopristin (adult dosage 7.5 mg/kg 3 times daily) is a new a intravenous antibiotic that is effective against most MRSA strains. It does not show cross-resistance with other classes of antibiotics.[130]

5. *Achromobacter (Alcaligenes) xylosoxidans*

5.1 Background

Alcaligenes xylosoxidans was transferred to the genus *Achromobacter* in 1998 as *Achromobacter xylosoxidans*.[132] It is an oxidase-positive, motile, Gram-negative bacillus. It has been isolated from the gastrointestinal tract of humans and from various hospital and environmental water sources. The genus comprises three main species: *A. xylosoxidans*, *A. ruhlandii* and *A. piechaudii*.[132] They can cause infection in a variety of situations[133] including bacteremia[134] and meningitis[135] in susceptible hosts, keratitis in contact lens wearers[136] and pulmonary exacerbations in patients with CF.[137]

5.2 Prevalence in Cystic Fibrosis Population

The prevalence of airway colonization with *A. xylosoxidans* was reported to be 8.7% in a recent large cross-sectional study at 69 CF centers in the US.[75] Tan et al. found a prevalence of 2.3% for chronic colonization and approximately 10% for intermittent colonization in a clinic population of 370 children and adults.[138]

5.3 Clinical Consequences of Colonization

A. xylosoxidans has been associated with acute respiratory exacerbations in two studies, but 14 of the 16 patients were concurrently colonized with *P. aeruginosa*.[132,137] Tan et al. documented a case-control study of chronic colonization in a series of patients with CF over a 2-year period. There was no significant difference in changes of respiratory function and various other clinical parameters between the index cases and controls.[138] Moissenet et al.[137] reported only one of eight pediatric patients with *A. xylosoxidans* who showed deterioration in nutritional status and chest radiograph appearance. This child was also colonized with *P. aeruginosa*. Two brothers with chronic *A. xylosoxidans* infection showed no deterioration in lung function over 3 and 6 years, respectively. The authors suggested that there is no need for aggressive antibiotic treatment to try to eradicate *A. xylosoxidans* infection.[139] However, we believe that studies aimed at investigating the clinical effect of chronic and low-grade infections would need to be large and long term to show any significant effect. Such studies are unlikely to be undertaken for this uncommon infection.

5.4 Management

There is no evidence that *A. xylosoxidans* is readily transmissible between patients.[140] Krzewinski and colleagues[79] described several instances of shared genotype, the majority of which were from siblings or patients otherwise epidemiologically linked. There are no controlled trials investigating the treatment of patients chronically colonized with species of *Alcaligenes*. Most of those infected with *A. xylosoxidans* are concurrently infected with *P. aeruginosa*.[133,138] It is reasonable to treat such patients with regular nebulized antibiotics, usually colistin 2 megaunits (160mg) twice daily, and 3-monthly courses of intravenous antibiotic,[141,142] the choice of which should be determined by bacterial resistance patterns to both *P. aeruginosa* and *A. xylosoxidans*. If the latter is the sole pathogen in a symptomatic patient showing a decline in respiratory function tests or worsening chest radiograph, *A. xylosoxidans* should be treated in a similar way to *P. aeruginosa* infection with antibiotic choice guided by bacterial sensitivity patterns.

A. xylosoxidans is typically resistant to many antibiotics. In a large phase III national collaborative study 90% of strains were resistant to tobramycin.[143] Similar resistance results were reported by Dunne and Maisch,[133] who found 14.3% of strains sensitive to gentamicin and tobramycin, 85% susceptible to ceftazidime, cefoperazone, ticarcillin, piperacillin and azlocillin, 75% susceptible to imipenem, and 50% to ciprofloxacin. Analysis of 94 multidrug-resistant isolates at a referral laboratory showed imipenem and piperacillin to be the most active agents against *A. xylosoxsidans* with susceptibility rates of 44% and 40%, respectively.[144] In the same study, the combination of imipenem and amikacin or ticarcillin/clavulanic acid and tobramycin, exhibited the most consistent synergistic activity against 30% and 29% of *A. xylosoxidans* isolates, respectively.

6. Conclusion

It is probable that the prevalence of multidrug-resistant *P. aeruginosa* infection in patients with CF will increase along with patient longevity and increasing lifetime exposure to multiple antibiotics. Antimicrobial treatment against *P. aeruginosa* can nonetheless be effective by acting against bacterial virulence factors and by a synergistic effect with the use of antibiotic combinations. If empirical treatment choices are the only ones possible, meropenem, ciprofloxacin and tobramycin combinations should be considered first. There is an urgent need for further trials involving MCBT and aerosolized TOBI. Colistin is an available antibiotic of proven efficacy and safety. Resistance is very unusual. We recommend its wider application for the treatment of

resistant organisms. Macrolide therapy may be useful but is hitherto untried.

B. cepacia complex infection is difficult to treat because of innate bacterial resistance. Reducing patient-to-patient spread by strict segregation of patients infected with *B. cepacia* from other patients in the clinic is a vital control measure. Combination high-dose antibiotic therapy appears to be the most effective treatment for acute respiratory exacerbations. The choice of antibiotic should be guided by clinical response.

S. maltophilia is a multidrug-resistant bacterium of uncertain significance in the pathogenesis of CF lung disease. Most patients show transient colonization with no clinical deterioration. Others with chronic colonization over months have shown a gradual decline. Trimethoprim/sulfamethoxazole is the treatment of choice for significant infections, alone or in combination with other agents. However, there are no efficacy data for these treatment regimens in patients with CF.

We believe it is important to try to eradicate MRSA from patients with cystic fibrosis for the following reasons: chronic colonization of the lower airway is likely to be associated with symptoms and a decline in respiratory function; MRSA colonization of patients with CF poses a significant cross-infection risk to other patients; the future prospect of lung transplantation is significantly reduced if a patient is chronically colonized with MRSA; and segregation policies employed to reduce the spread of MRSA within the clinic inevitably result in feelings of isolation and stigmatization. Further research is required to determine the most successful regimen for eradicating chronic MRSA infection from patients with CF.

A. xylosoxidans is an uncommon chronic infection in patients with CF. There is little published evidence that it causes long-term lung damage, although most studies involve small patient numbers and are short term. In patients with CF, when *A. xylosoxidans* infection is associated with clinical decline and a fall in pulmonary function it seems reasonable to treat patients with appropriate antibiotics guided by bacterial resistance patterns.

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