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Mycoplasma Disease and Acute Chest Syndrome in Sickle Cell Disease

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ABSTRACT. *Background.* **Acute chest syndrome (ACS) is the leading cause of hospitalization, morbidity, and mortality in patients with sickle cell disease. Radiographic and clinical findings in ACS resemble pneumonia; however, etiologies other than infectious pathogens have been implicated, including pulmonary fat embolism (PFE) and infarction of segments of the pulmonary vasculature. The National Acute Chest Syndrome Study Group was designed to identify the etiologic agents and clinical outcomes associated with this syndrome.**

Methods. **Data were analyzed from the prospective study of 671 episodes of ACS in 538 patients with sickle cell anemia. ACS was defined as a new pulmonary infiltrate involving at least 1 complete segment of the lung, excluding atelectasis. In addition, the patients had to have chest pain, fever >38.5C, tachypnea, wheezing, or cough. Samples of blood and deep sputum were analyzed for evidence of bacteria, viruses, and PFE. *Mycoplasma pneumoniae* infection was determined by analysis of paired serologies. Detailed information on patient characteristics, presenting signs and symptoms, treatment, and clinical outcome were collected.**

Results. **Fifty-one (9%) of 598 episodes of ACS had serologic evidence of *M pneumoniae* infection. Twelve percent of the 112 episodes of ACS occurring in patients younger than 5 years were associated with *M pneumoniae* infection. At the time of diagnosis, 98% of all patients with *M pneumoniae* infection had fever, 78% had a cough, and 51% were tachypneic. More than 50% developed multilobar infiltrates and effusions, 82% were transfused, and 6% required assisted ventilation. The average hospital stay was 10 days. Evidence of PFE with *M pneumoniae* infection was seen in 5 (20%) of 25 patients with adequate deep respiratory samples for the PFE assay. *M pneumoniae* and *Chlamydia pneumoniae* was found in 16% of patients with diagnostic studies for *C pneumoniae*. *Mycoplasma hominis* was cultured in 10 (2%) of 555 episodes of ACS and occurred more frequently in older patients, but the presenting symptoms and clinical course was similar to those with *M pneumoniae*.**

Conclusions. ***M pneumoniae* is commonly associated with the ACS in patients with sickle cell anemia and occurs in very young children. *M hominis* should be considered in the differential diagnosis of ACS. Aggressive treatment with broad-spectrum antibiotics, including 1 from the macrolide class, is recommended for all patients as well as bronchodilator therapy, early transfusion, and respiratory support when clinically indicated.** *Pediatrics* **2003;112:87–95; *sickle cell, acute chest syndrome*, Mycoplasma pneumoniae, Mycoplasma hominis, *pulmonary fat embolism, pneumonia*.**

ABBREVIATIONS. ACS, acute chest syndrome; PCR, polymerase chain reaction; PFE, pulmonary fat embolism; SCD, sickle cell disease; VOC, vaso-occlusive crisis; Ig, immunoglobulin; IL, interleukin.

Acute chest syndrome (ACS) is the leading cause of mortality and morbidity in patients with sickle cell anemia. Radiographic and clinical findings in ACS resemble pneumonia; however, etiologies other than infectious pathogens have been implicated including pulmonary fat embolism (PFE) and infarction secondary to vaso-occlusion of segments of the pulmonary vasculature. Recently, the findings of the National Acute Chest Syndrome Study Group were reported.[1] This multicenter prospective study of 671 episodes of ACS in 538 patients was designed to determine the causes, clinical outcome, and prognostic factors associated with this syndrome. An etiologic agent (either infectious or PFE) was identified in 38% of episodes. One of the most frequent infections associated with ACS was *Mycoplasma pneumoniae*.

The identification of *M pneumoniae* infections in studies of community acquired lower respiratory tract infections in previously healthy patient groups has ranged from 1% to 30% and tends to be higher in outpatients and in school-aged children than in other age groups.[2–19] Epidemics of *M pneumoniae* infection have also been reported.[20–22] The hospital course of patients with lower respiratory infection secondary to *Mycoplasma* ranges from outpatient treatment with antibiotics to prolonged hospitalizations in the elderly and patients with underlying medical conditions. Although not common, respiratory failure has been documented even in previously healthy patients.[23–25] In addition to pneumonia, *M pneumoniae* has also been associated with pharyngitis, bronchitis,[26] asthma,[27,28] bronchiolitis obliterans,[29,30] acute respiratory distress syndrome,[24,31,32] pericardi-

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tis,[33–35] mediastinitis,[36] arthritis,[37,38] Stevens-Johnson syndrome and erythema multiforme,[39,40] erythema nodosum,[41] meningoencephalitis,[42–45] and stroke.[46] Rarely, deaths have been attributed to *Mycoplasma* infections.[6,25,33,47]

There have been only a few reports where *Mycoplasma* has been associated with ACS in limited numbers of sickle cell patients,[48–55] and in many, the clinical outcome of these cases was not fully characterized. The purpose of this report is to describe the incidence and clinical course of *M pneumoniae* infection in sickle cell disease (SCD) patients with ACS from the National Acute Chest Study Group. We also summarize the clinical outcome of a small group of patients found to have infection with *Mycoplasma hominis*.

METHODS

Patients from 30 centers were eligible if they had an electrophoresis of hemoglobin SS, hemoglobin SC, or hemoglobin SB thalassemia, were diagnosed and hospitalized with ACS, and had signed informed consent. ACS was defined as a new pulmonary infiltrate involving at least 1 complete segment consistent with alveolar consolidation, excluding transient atelectasis. In addition, the patients had to have chest pain, fever >38.5°C, tachypnea, wheezing, or cough. From March 1993 through March 1997, 671 episodes of ACS in 538 hospitalized patients were enrolled.

A standardized treatment and monitoring protocol was used.[1] Patients were transfused at the discretion of the attending physician for improvement of respiratory status. Transfusion guidelines and methods for identification of alloantibodies have previously been described.[1] Standardized forms were used to document medical history, daily physical examinations, radiographs, oxygenation status, transfusions, bronchoscopy complications, and follow-up.

Blood cultures were obtained before the initiation of therapy whenever possible. Bronchoscopy or sputum samples were obtained when possible for aerobic and anaerobic cultures at the participating centers. A bacterial etiology was determined if there was a positive blood culture or heavy growth of an organism from a bronchial or sputum culture with correlative Gram-stain results. Bronchial, sputum, and nasopharynx samples were also sent to Dr. Lennette's central laboratory for standard viral and *Mycoplasma* cultures.[56–58] All viral and *Mycoplasma* culture isolates were identified by immunofluorescent staining with specific reagents. Specifically, *M pneumoniae* and *M hominis* were cultured on SP4 medium as described.[59] Isolates were identified by immunofluorescence staining with fluorescein isothiocyanate-conjugated monospecific antisera provided by Dr J. Tully from the National Institutes of Health.

Legionella pneumophila serogroups were detected by indirect immunofluorescent staining, and respiratory syncytial virus was detected using a direct immunofluorescent antibody technique.

Infection with *M pneumoniae* was determined by comparing immunoglobulin (Ig) G antibody titers between the acute and convalescent phase of the illness. Only patients with paired serologies within 3 months after the diagnosis of ACS were included in this analysis; patients with only a single IgG titer were excluded. An immune adherence assay was used,[58] and a 4-fold rise in IgG titers was considered evidence of *M pneumoniae* infection. In those patients with high standing IgG titers (IgG levels ≥1024), acute serum was analyzed for the presence of IgM antibodies with an enzyme immunoassay for *M pneumoniae* (ImmunoWell; Gen Bio, San Diego, CA). Those patients with high standing titers and detectable IgM antibodies were considered acutely infected with *M pneumoniae*. Indirect immunofluorescence assays were used for the diagnosis of parvovirus B19 and Epstein-Barr virus.[60,61]

After the study was already underway, diagnostic techniques became available for the diagnosis of *C. pneumoniae* infection. Respiratory and paired serology samples were then sent to the laboratory of Dr. J. Schachter for *Chlamydia* culture and analysis of antibody titers by the microimmunofluorescence technique.[62] Nonreplicated nasopharynx samples were further analyzed by Dr. D. Dean using the polymerase chain reaction (PCR) for *C. pneumoniae*.[63] The diagnosis of *C. pneumoniae* infection was made if there was a positive culture, a positive PCR, a 4-fold change in IgG titers, or a high standing IgG titer.[1]

Intracellular lipid from alveolar macrophages obtained from bronchial samples was evaluated for evidence of PFE according to a modification of the Corwin index.[64] Findings from autopsies and histopathology slides were analyzed by the pathology unit for SCD in Alabama.

Statistical Analysis

For comparisons of categorical clinical data between the patients with *M pneumoniae* and *M hominis*, a χ^2 analysis with a continuity adjustment was used. All confidence intervals were 2-sided and a P value of .05 was considered statistically significant. For comparison of continuous variables, we used the Kruskal-Wallis test.

RESULTS

M pneumoniae

Paired serologies were analyzed for *M pneumoniae* from 598 episodes of ACS in 484 patients: results were positive from 51 episodes (9%). No patient had a documented recurrent *M pneumoniae* infection. In 31 of these 51 patients, a 4-fold rise in IgG titers from the acute to convalescent phase was documented. In the remaining 20 patients, paired IgG titers were greater than or equal to 1024 and the acute serology was positive for IgM. Of the 51 patients with serologic evidence of *M pneumoniae* infection, 26 patients underwent bronchoscopy and sputum was collected in another 20. The assay for PFE was not interpretable in 50% of the sputum samples because of inadequate sampling of the lower respiratory tract. However, there was evidence of PFE in 5 (20%) of 25 deep respiratory samples available for analysis. In addition, *C pneumoniae* was found in 5 (16%) of 32 *M pneumoniae* patients with diagnostic tests for *Chlamydia*. Other pathogens identified from bronchial or blood cultures in the 51 patients with *M pneumoniae* were: rhinovirus, respiratory syncytial virus, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*. A total of 9 patients with *M pneumoniae* had evidence of infection with other pathogens.

The incidence of *M pneumoniae* was higher in younger patients. *M pneumoniae* was diagnosed in 12% of the 112 episodes in patients below the age of 5, 14% of the 181 episodes in patients ages 5 to 9.9, 6% of the 98 episodes in patients 10 to 14.9, and in only 3% of the 207 episodes in the 15 and over age group. The demographic characteristics of the patients with *M pneumoniae* infection are given in Table 1. The average age of the patients with *M pneumoniae* was 9.7 years (range: 1.6–47.9 years). Fifty-three percent of the patients were female. Most patients had prior serious complications of SCD. Seventy-six percent of the patients had a history of ACS, 72% vaso-occlusive crisis (VOC), and 24% major surgery. At the time of diagnosis of ACS, 98% of patients had a fever, 78% had a cough, 51% were tachypneic, 44% had chest pain, and 39% had abdominal pain. The patients' hemoglobin had declined 1.0 g/dL on average, and the mean white blood cell count was 21 300. Two thirds of the patients were admitted to the hospital with the diagnosis of ACS, whereas 33% developed ACS after admission for another problem

TABLE 1. Demographic and Clinical Characteristics of SCD Patients With ACS Associated With *M pneumoniae* or *M hominis*

	M pneumoniae ($N = 51$)		*M hominis* ($N = 10$)		*P* Value
Gender					NS*
Male	24/51	47%	5/10	50%	
Female	27/51	53%	5/10	50%	
Hemoglobin type					NS
SS	41/51	80%	6/10	60%	
Other variants	10/51	20%	4/10	40%	
Mean age	9.7		18.6		.004
0–1.9	2/51	4%	0/10	0%	NS
2.0–4.9	11/51	22%	1/10	10%	NS
5.0–9.9	25/51	49%	1/10	10%	.05
10.0–14.9	6/51	12%	1/10	10%	NS
15.0–19.9	3/51	6%	2/10	20%	NS
20+	4/51	8%	5/10	50%	.003
Past medical					
VOC	36/50	72%	7/10	70%	NS
Transfusion	36/51	71%	7/10	70%	NS
ACS/pneumonia	39/51	76%	7/10	70%	NS
Prophylactic antibiotics at admission	39/51	76%	5/10	50%	NS
Major surgery	12/51	24%	4/10	40%	NS
Neurologic disease	8/46	17%	3/8	38%	NS
Sleep apnea	5/51	10%	2/9	22%	NS
RBC antibodies	7/50	14%	1/10	10%	NS
Asthma	6/51	12%	2/10	20%	NS
Aseptic necrosis/fracture	4/51	8%	1/10	10%	NS
Renal disease/urinary tract infection	3/50	6%	1/10	10%	NS
On chronic transfusion	2/51	4%	2/10	20%	NS
Cardiac disease	1/51	2%	0/10	0%	NS
Chronic lung disease	2/51	4%	1/10	10%	NS
Smoking	0/51	0%	4/10	40%	.0001
Reason for this admission					
ACS	34/51	67%	6/10	60%	NS
Other	17/51	33%	4/10	40%	
ACS					
Fever	50/51	98%	9/10	90%	NS
Cough	40/51	78%	5/10	50%	NS
Chest pain	22/50	44%	4/10	40%	NS
Tachypnea	26/51	51%	2/10	20%	NS
Shortness of breath	18/49	37%	4/10	40%	NS
Abdominal pain	20/51	39%	3/10	30%	NS
Extremity pain	9/50	18%	4/10	40%	NS
Rib/sternal pain	5/51	10%	2/10	20%	NS
Asthma/wheezing	6/49	12%	0/10	0%	NS
Neurologic dysfunction	3/51	6%	2/10	20%	NS
Heart failure	1/51	4%	0/10	0%	NS

RBC indicates red blood cells.
* NS indicates *P* value > .05.

(mostly VOC). Only 1 patient in this study was admitted for elective surgery and went on to develop ACS.

During their hospitalizations, patients developed multilobar disease which was associated with effusions in over half of the patients (Table 2). Empyema was diagnosed in 1 patient and necessitated chest tube placement. Eighty-four percent of patients required oxygen, and 78% were administered bronchodilators. All patients were treated with antibiotic: 92% were treated with erythromycin and 94% with a cephalosporin. Eighty-two percent received transfusions. Complications recorded during the patients' hospitalization are shown in Table 2. Three of the patients (6%) with *M pneumoniae* required mechanical ventilation. All 3 were started on erythromycin and bronchodilators, and received transfusions early in their course. Despite this, one 3-year-old boy went on to develop acute respiratory distress syndrome, was intubated for 3 weeks, and was diagnosed with global cognitive impairment presumed to be secondary to anoxic brain injury. A 7-year-old girl developed respiratory failure on the second hospital day and required high-frequency jet ventilation. *S aureus* was cultured from a bronchoscopy specimen, and in addition to ceftriaxone and clarithromycin, she was treated with nafcillin. A third patient was intubated for 1 day after developing laryngospasm and significant hypoxia after bronchoscopy. The average hospital stay for patients infected with *M pneumoniae* was 9.8 days.

M hominis

Cultures were positive for *Mycoplasma* species in 12 of 555 of these episodes of ACS. In 10 episodes, *M hominis* was identified by culture and serologies were not consistent with an acute *M pneumoniae* infection; *M pneumoniae* was identified in the remaining 2 episodes. Eight of the 10 patients grew *M hominis* from deep sputum and 2 from bronchoscopy samples.

TABLE 2. Hospital Course of Patients With ACS Associated With *M pneumoniae* or *M hominis* Infection

	M pneumoniae ($N = 51$)		*M hominis* ($N = 10$)		*P* Value**
Laboratory values at diagnosis of ACS					
Mean hemoglobin	7.2 g/dl		7.8 g/dl		NS
Mean change in hemoglobin from baseline	−1.00		−1.20		NS
Mean white blood cell count	21 300		22 700		NS
Number of lobes involved on chest radiograph	1.6		1.3		NS
Presence of effusion	14/41	34%	2/10	20%	NS
Mean room air oxygen saturation*	92%		94%		NS
Examination findings during hospitalization					
Respiratory rate >30	38/51	75%	4/10	40%	NS
Mean peak respiratory rate	39		32		NS
Mean peak temperature	39.0		39.0		NS
Rales	46/51	90%	9/10	90%	NS
Decreased breath sounds	45/51	88%	9/10	90%	NS
Wheezing	18/51	35%	1/10	10%	NS
Nasal flaring	15/51	29%	1/10	10%	NS
Max number of lobes (anytime)	2.1		1.8		NS
Any lower lobes	45/50	90%	8/9	89%	NS
Any middle lobes	32/50	64%	4/7	57%	NS
Any upper lobes	18/50	36%	3/8	38%	NS
Effusion (anytime)	30/50	60%	4/10	40%	NS
Treatment during hospitalization					
Erythromycin	47/51	92%	9/10	90%	NS
Cephalosporin	48/51	94%	10/10	100%	NS
Other antibiotic	16/48	33%	2/9	22%	NS
Oxygen	43/51	84%	9/10	90%	NS
Transfused	42/51	82%	8/10	80%	NS
Bronchodilator	40/51	78%	7/10	70%	NS
Ventilator	3/51	6%	1/10	10%	NS
Complications (%)					
Vaso-occlusive event	20/51	39%	6/10	60%	NS
Abdominal pain	26/51	51%	4/10	40%	NS
Pulmonary‡	4/51	8%	1/10	10%	NS
Neurologic§	3/51	6%	2/10	20%	NS
Cardiac¶	4/51	8%	0/10	0%	NS
Renal‖	1/51	1%	0/10	0%	NS
Death	0/51	0%	0/10	0%	NS
Total number of days hospitalized (mean)	9.8		13.1		NS

* Over 50% of the patients had missing oxygen saturation data.
‡ Includes respiratory failure and empyema.
§ Includes anoxic brain injury, seizure, altered mental status, and severe headache.
¶ Congestive heart failure.
‖ Pyelonephritis.
** NS indicates *P* value > .05.

Three of these 10 patients had been previously enrolled in the study, and other etiologies of ACS had been identified; none of the patients had evidence of recurrent *M hominis*. Multiple pathogens were identified in 2 patients with *M hominis*: *M hominis* with rhinovirus in 1 patient and *M hominis* with *Enterobacter*, *S aureus*, and PFE in the other. PFE alone with *M hominis* was found in a third patient.

The average age of the 10 patients with *M hominis* was significantly higher than those with *M pneumoniae* (18.6 vs 9.7, $P = .004$). The rate of VOC was higher (60% vs 39%) and the duration of hospitalization was longer in the *M hominis* group (13.1 vs 9.8 days), but these differences were not statistically significant. One patient required mechanical ventilation for 3 weeks, was diagnosed with multi-organ dysfunction, and discharged after a 2-month hospitalization.

DISCUSSION

Using paired serologies, we identified *M pneumoniae* in 9% of the episodes of ACS. The current reference laboratory diagnosis of *M pneumoniae* is by serology based on 4-fold titer changes.[65] Our immune adherence assay is a complement fixation assay modified to increase the sensitivity by 8-fold, on par with enzyme immunoassays. Culturing *M pneumoniae* is problematic, as the organism is both fastidious and difficult to recover from mixed flora because of its slow growth (only microcolonies in weeks). In contrast, *M hominis* is a much faster growing organism. The combination of an insensitive culture and the very short window during which the organisms are recoverable are the reasons why cultures are considered unreliable, and most likely why we were only able to isolate *M pneumoniae* from 2 of the respiratory samples in this study. Also, many of the patients were begun on macrolide antibiotics when diagnosed with ACS (before bronchoscopy or sputum sampling). Previous studies of pneumonia in pediatric patients without SCD reported rates of *M pneumoniae* infection from 9% to 27%.[2,8,13,66] This range of estimates may reflect different patient populations (inpatient vs outpatient), diagnostic meth-

ods, and seasonal variation.[5,20–22] In addition, recent studies have employed PCR techniques for the identification of *M pneumoniae*; however, there isn't always agreement between serologic methods and the newer PCR techniques, which have not been standardized.[2,44,66–71] Clearly, there are limitations to all of these diagnostic techniques and caution must be used when interpreting data based solely on serologic methods, as in our study.

Several studies have identified *M pneumoniae* in small groups of SCD patients with ACS.[49,53–55,72–75] Incidences of *M pneumoniae* associated with ACS have been in the range of 13% to 18% of episodes.[55,73–75] These studies were in smaller groups of patients and employed different diagnostic criteria than those used in our study. In patients with pneumonia, mixed infections with *M pneumoniae* have been previously reported.[9,76] In our study, we also had several patients with evidence of other infectious pathogens, such as *C pneumoniae*. In these cases, it is difficult to conclude which pathogen is primarily associated with ACS, or if these are truly "mixed infections". To our knowledge, PFE and *Mycoplasma* infection have not been previously reported in patients with SCD. Unfortunately, our sample size did not permit a comparison of disease severity between this group and those without PFE.

The youngest patient with *M pneumoniae* in this study was 1.6 years. Although *M pneumoniae* is rarely seen in infants,[77,78] Waris et al[16] did identify it in a 6-month-old with pneumonia. In contrast to other reports where *M pneumoniae* was more common in older children and adolescents,[8,13,16,75] the incidence of *M pneumoniae* in children under 5 (12%) in our population was similar to that in the 5- to 10-year-olds (14%).

Pneumonia associated with *M pneumoniae* infection is commonly treated on an outpatient basis,[2,12,77,79] and this organism has been identified in asymptomatic children in child care.[80] However, some reports have documented respiratory failure and death attributed to *M pneumoniae* infections.[6,23,25,47,81] One study of adults hospitalized for pneumonia documented a respiratory failure rate of 10% in patients presumed to have *M pneumoniae*. Several of these patients were elderly or had underlying illnesses. There are also case reports of severe *M pneumoniae* infection in children with SCD.[50,53,82,83] We found even higher rates of multilobe involvement, pleural effusion, and transfusion requirements in our patients with ACS associated with *M pneumoniae* than in previous studies.[53,74,75] Additionally, 3 patients (6%) in our study developed respiratory failure despite aggressive therapy. The average hospital stay of 10 days and associated complications reflect the severity of this syndrome.

Evidence of the cytotoxic effects of *M pneumoniae* in the respiratory tract has been previously deduced from electron microscopy, biopsy, and autopsy studies.[84–87] This process and the subsequent inflammatory response—including infiltration of lung parenchyma with lymphocyte, monocyte, and natural killer cells and the production of proinflammatory cytokines[88,89]—may lead to damage of vascular endothelium, alteration of cellular adhesion properties, regional hypoxia, and further stimulation of cytokine release. In sickle cell patients, these factors can precipitate irreversible sickling and pulmonary entrapment of erythrocytes.[90–92] The ability of *M pneumoniae* to stimulate cytokine production has been documented in several recent reports. In one study, total white blood cell count and cytokines involved in regulation of neutrophil function, interleukin (IL)-8, and granulocyte colony-stimulating factor were found to be higher in patients with bacterial pneumonia; the subset of patients with *M pneumoniae* had similar IL-8 levels to those with pneumococcal pneumonia.[93] Other cytokines, such as IL-6, have been shown to be associated with severity of pneumonia secondary to *M pneumoniae* infection[94] and indicators of clinical recovery.[95] Serum adenosine deaminase and free IL-2 receptor levels have been reported to be high in cases of *M pneumoniae* and useful in distinguishing them from other causes of bacterial pneumonia.[96] Furthermore, in a study of cytokine levels in bronchalveolar lavage fluid, IL-2, IL-4, and IL-4/interferon-γ ratios were higher in patients with *Mycoplasma* than in controls, a response consistent with promotion of IgE production.[97] In contrast, depressed cellular immunity in patients with *M pneumoniae* has been previously shown.[98] In his review, Overturf[99] described a variety of immunologic abnormalities in patients with SCD. Recently, lymphocytic blastogenic responses and interferon-γ production in vitro have been shown to be significantly decreased in SCD patients with acute pulmonary infections.[100] Although the interpretation of the data on the role of cell-mediated and humoral immunity in response to *M pneumoniae* infection is controversial, the immunologic abnormalities exhibited by patients with SCD likely contribute to the clinical severity of *M pneumoniae* infection in this population.

Three fourths of the children in this study had experienced major complications of SCD, including VOC and previous episodes of ACS. Twelve percent also had a history of asthma and 36% had wheezing during their hospitalization. *Mycoplasma* may exacerbate asthma[2,27,68,101] and precipitate wheezing in nonasthmatic patients who may then exhibit abnormal lung function years after the initial infection.[101–103] The association between reactive airway disease and *M pneumoniae* infection suggests a role for bronchodilator treatment in the management of ACS attributed to *M pneumoniae*. The most widely recommended treatment of *M pneumoniae* infection is the use of macrolide antibiotics. Although it has occasionally been shown to be resistant to erythromycin,[102,104–108] the clinical efficacy of erythromycin and other macrolide antibiotics has been repeatedly demonstrated.[2,8,109,110] Several reports have also shown better outcomes in patients treated with erythromycin early in the course of their infection.[102,111] The duration of treatment is unclear as studies have shown clinical efficacy in the face of persistent positive cultures from upper airway sites.[8,107,108] Standard regimens for treatment of *M pneumoniae* have been 30 to 50 mg/kg divided 2 to 4 times per day for 10 days.[112] Azithromycin, 10

mg/kg on the first day and 5 mg/kg per day for 4 additional days, has also been shown to be equally efficacious.[8] Other antibiotics for the treatment of *M pneumoniae*, including fluoroquinolones, have been studied.[14,113–117] We recommend that all patients, even infants, with ACS be treated with an antibiotic from the macrolide class and a broad spectrum cephalosporin as well as bronchodilators, oxygen, and transfusion when necessary. However, tetracycline should not be used in children under the age of 8,[112] and fluoroquinolones have not been approved for use in children. High-dose prednisone has also been used for the treatment of major complications from *M pneumoniae*.[31,118,119]

M hominis infection is most commonly seen in the genitourinary tract. Uncommonly, *M hominis* has been associated with infections outside the genitourinary tract and has been seen in immunocompromised patients and those recovering from thoracic or transplant surgery.[34,36,120–123] In his review, Mufson[123] noted that isolation of *M hominis* from the upper respiratory tract in adults and children with chronic tonsillitis may represent carriage of but not infection with this organism. *M hominis* pneumonia is seen in neonates and recently has been identified in a few cases of lower respiratory infections in older children and adults.[77,124] Although less likely, deep sputum and bronchoscopy samples may be contaminated by organisms in the oropharynx, so isolation of *M hominis* from these samples may not represent a true pathogen. Interestingly, the average age of the patients in our study with *M hominis* was 19.

M hominis has been shown to be resistant to erythromycin in vitro.[114,117] The minimum inhibitory concentrations of tetracycline appear to be superior, but there is a concern for resistant organisms.[114,125,126] Other classes of antibiotics such as the glycylcyclines and fluoroquinolones have shown in vitro activity against *M hominis*.[110,113,115,126–128] Although *M hominis* was cultured in only 2% of the episodes of ACS in our study, it was associated with significant morbidity and should be considered in the treatment of ACS. Given the small number of patients in whom *M hominis* was isolated, the comparison of patient demographics, presenting symptoms, response to antibiotics, and clinical course between those patients with *M pneumoniae* and those with *M hominis* is inadequate. Clearly, further studies are needed.

CONCLUSIONS

We found serologic evidence of *M pneumoniae* in 51 (9%) of 598 episodes of ACS in patients with SCD. In fact, 12% of episodes of ACS in patients younger than 5 years were associated with *M pneumoniae*. All patients were hospitalized for an average of 10 days, and there was a high rate of complications including assisted ventilation in 6%. Nine patients with *M pneumoniae* also had evidence of infection with other pathogens, and 5 had PFE. *M hominis* was cultured in 10 additional patients and they tended to be older than those with *M pneumoniae*. Although serologic methods are limited and isolation of an organism from respiratory samples may represent colonization, we believe *M pneumoniae* and *M hominis* should be considered in the treatment of ACS. ACS is a multifactorial syndrome often precipitated by an infectious process that causes cellular destruction, inflammation, and regional hypoxia that leads to erythrocyte sickling and further sickle cell-related injury. All SCD patients with ACS, including children under the age of 5 years, should be treated with broad-spectrum antibiotics, including 1 from the macrolide class. Additionally, bronchial hyperreactivity is common and bronchodilator therapy is usually indicated. We recommend early leukocyte-depleted, matched, simple transfusions for patients with significant anemia, multilobar pneumonia, any signs of respiratory distress on oxygen, and those at risk for complications.

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THE TEST OF A SOCIETY

"The ethical and legal tone of a society can best be judged by how it treats the weakest, neediest, and most vulnerable members. In our Western societies, many of us experience such vulnerability only when we are sick."

Somerville M. *The Ethical Canary*. Viking; 2000

Submitted by Student

Mycoplasma Disease and Acute Chest Syndrome in Sickle Cell Disease

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