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INCIDENCE, MANAGEMENT, AND OUTCOME OF CHILDHOOD EMPYEMA: A PROSPECTIVE STUDY OF CHILDREN IN CAMBODIAN REFUGEE CAMPS

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Abstract. To determine the incidence, outcome, and optimal management of empyema, all children less than 15 years of age admitted to Khao-I-Dang Hospital with a diagnosis of empyema during a 23-month period were prospectively studied. Khao-I-Dang Hospital provides care to 137,000 Cambodian children residing in eight refugee camps along the Thai-Cambodian border. Ninety-eight children with empyema were identified, for an annual incidence of 0.37 cases per 1,000 children. All patients had chest tubes inserted on admission, and all were treated with parenteral antibiotics, which included chloramphenicol in 92% of the patients and cloxacillin in 72%. Patients were hospitalized a mean of 30 days, and chest tubes were in place for a mean of 12 days. Surgery was performed on four patients who had bronchopleural fistulas that persisted for more than 14 days. Only one (1%) of the 70 patients treated with cloxacillin required thoracotomy, compared with three (11%) of the 28 patients who did not receive cloxacillin ($P = 0.07$). In a multiple regression analysis, the presence of pneumatoceles or mediastinal shift on admission chest radiograph, a history of tuberculosis in the family, and an age of more than five years were predictive of a longer duration of chest tube drainage. No patient died in the hospital, and only one patient died in the six months following discharge from the hospital. Chest radiographs that were obtained six months after discharge in 25 patients were all essentially normal, despite marked abnormalities on chest radiographs obtained at discharge. In summary, conservative medical management with the use of chest tubes for these 98 children with empyema resulted in a mortality rate of 1.0%, and should be considered as an effective alternative to the surgical management of patients presenting with this complication.

Acute infections of the lower respiratory tract are, along with diarrhea, the commonest causes of death in children older than one month of age in developing countries.[1] Although the precise cause of death from respiratory tract infection in children living in developing countries is uncertain, empyema is known to be one of the most serious complications of acute lower respiratory tract infections. Though empyema still occurs among children with pneumonia in developed countries,[2–5] it is thought to be more common among children in the tropics.[6–8] Possible reasons for this include household crowding leading to increased transmission of respiratory pathogens and higher incidence rates of pneumonia, parental delay in seeking care for children with respiratory symptoms, the lack of readily available health care services, or the absence of appropriate antimicrobial agents for the treatment of pneumonia.[9–11] Host factors, including poor nutrition, may also play a role.[12, 13]

The currently recommended therapy for empyema is insertion of a chest tube and provision of appropriate antimicrobial therapy.[14–19] The choice and duration of antimicrobial therapy, the duration the chest tube should remain in place, the indication for replacing or removing of chest tubes, and the indications for surgical decortication have not been well defined. Although children with empyema are routinely given four or more weeks of antimicrobial therapy, much of it parenterally, the need for this has not been well documented. Factors influencing therapy include the infecting organism (infections due to *Staphylococcus aureus* are usually more severe and require a longer duration of antimicrobial therapy and hospital stay) and the resources available for patient care.[4] In developing countries, where resources for medical care are severely limited, long term hospitalization, provision of parenteral antibiotics, and surgical intervention are often not possible. Therefore, it is important to establish

the least expensive, but still effective, means of managing this disease.

Almost all previous studies of the management of empyema are retrospective analyses of patients admitted over a number of years.[8, 16, 17, 20] This study reports the results of a prospective analysis of all children with empyema residing in the eight refugee camps served by Khao-I-Dang Hospital, and the results of a standard, simple regimen used to treat these children.

PATIENTS AND METHODS

Study site and patient population

This study was conducted at the Khao-I-Dang refugee camp, which is located in eastern Thailand six kilometers from the Cambodian border. This camp was established in 1979 and is home to 10,000 persons. Khao-I-Dang camp houses the only referral hospital for the 300,000 Cambodians refugees and displaced persons, including 137,000 children less than 15 years of age, who live in the eight Khmer refugee camps along the Thai-Cambodian border. All seriously ill patients from these camps, including those patients requiring surgery, insertion of a chest tube, oxygen, or a blood transfusion, are transferred to Khao-I-Dang Hospital. Two humanitarian organizations, the International Committee of the Red Cross (ICRC) and Medecins Sans Frontieres are responsible, respectively, for providing surgical and medical care at the Khao-I-Dang hospital. The hospital contains 300 beds and is staffed by 25 expatriate doctors and nurses and 200 local staff, including 30 paramedics. All care is provided free of charge. Children residing in these camps were routinely given BCG vaccine at birth or when they are first arrive in the camp, but were not immunized against *Hemophilus influenzae.*

Study protocol

Case definition. From July 1989 through May 1991, all children less than 15 years of age who were suspected of having an empyema had a thoracentesis done on admission to the Khao-I-Dang Hospital. Empyema was considered to be present if gross pus was aspirated from a thoracentesis performed at this hospital. All such patients were entered into the study.

Initial evaluation. Histories were obtained and physical examinations were performed on all patients on admission to the hospital. Information recorded included age and gender, prior treatment for the current illness, a history of family members with tuberculosis, vital signs, and findings on chest examination. Nutritional status was determined using weight-for-age criteria based on the percentage of the National Center for Health Statistics (Rockville, MD) median weight-for-age.[21] Children who were less than 60% of the median weight-for-age were considered to be severely malnourished. All patients had a complete blood count and erythrocyte sedimentation rate determined on admission. Facilities for culture of pleural fluid or for biochemical analysis of the fluid were not available.

Chest radiographs. Chest radiographs were obtained on admission (in most cases before the thoracentesis), after insertion of the chest tube, before removal of the chest tube, at discharge, and at follow-up six months after discharge from the hospital. All chest radiographs were taken in the posterior-anterior position, with only a limited number of patients also having a lateral chest radiograph obtained. All chest radiographs were reviewed by an experienced pediatric radiologist (RGKM) and two other members of the study team (ALF and MLB). Chest radiographs were evaluated as to the location and size of the pleural effusion (large when there was complete opacification of the hemithorax, medium if the effusion covered one-third or more of the hemithorax, and small if less than one-third of the hemithorax was covered), the presence and location of pulmonary infiltrates, and the presence of a mediastinal shift, pneumatoceles, or air in the pleural space.

Use of chest tubes and indications for surgery. If an empyema was diagnosed, a chest tube was inserted under local anesthesia through the fifth or sixth intercostal space in the mid-axillary line. The chest tube was connected to an underwater seal, and continuous suction was applied in those patients who had evidence of lung collapse on chest radiograph. Criteria for removing functioning chest tubes were < 50 ml of drainage in 24 hr, absence of bronchopleural fistula as evidenced by the absence of bubbles in the drainage bottle during expiration, and determination that the lung was expanded on the chest radiograph. Patients who had a loculated empyema that was not drained by the initial chest tube had an additional chest tube inserted. Surgical decortication was performed when there was evidence of a persistent bronchopleural fistula and accompanying lung collapse.

Antimicrobial therapy. Parenteral antimicrobial therapy was provided for all patients for at least seven days. Parenteral therapy was continued for more than seven days in patients who remained febrile, and was only discontinued when a patient had been afebrile for 48 hr. Following parenteral therapy, all patients received an additional three weeks of oral antimicrobial therapy, so that all patients received at least four weeks of therapy. The choice of antimicrobial agents was made by the physician caring for the patient. In almost all cases, patients received chloramphenicol, usually in combination with cloxacillin or penicillin.

Criteria for discharge. Patients were discharged when the chest tube had been removed for at least one week, they were afebrile, and they had no respiratory symptoms.

Follow-up examinations. All patients were requested to return for a follow-up visit six months after discharge. For patients residing in camps other than Khao-I-Dang, this was often difficult because travel between camps was restricted and required the approval of the Thai Army and the ICRC. The customary policy was that only patients who were acutely ill could leave their camp for medical care. For patients unable to return for a follow-up visit, the death and tuberculosis registers of the outlying camps were reviewed at the end of the study. These registers contain a list of all patients who have died, and who have received therapy for tuberculosis. There was little emigration from the camps during this period; thus, any death among study participants would have been recorded.

Statistical methods

Data was entered into a computer and analyzed using Stata (Computing Resource Center, Santa Monica, CA), a statistical program for personal computers. Differences in proportions were tested for significance using the chi-square test, or Fisher's exact test when the predicted size of any cell was five or less. Student's t-test was used to test the significance of differences in group means. All tests of significance were two-tailed. Linear regression analysis was used to determine which variables were independently associated with the severity of the hospital course, as indicated by the length of time a chest tube remained in place. Variables chosen to be evaluated in the regression analysis were those that were significant on univariate analysis, or those that might logically be expected to affect duration of chest tube drainage. Variables tested in the regression analysis were age, sex, disease duration before hospitalization, history of tuberculosis in the family, physical examination and radiographic findings, absolute blood neutrophil count, and erythrocyte sedimentation rate. Multiple models were evaluated, and the final model included those variables that were predictive at the $P < 0.1$ level.

RESULTS

During the 23-month study period, 98 children less than 16 years old were diagnosed as having empyema. Two of these children were resident in the Khao-I-Dang camp. Eighty nine (91%) of the 98 patients were referred from either the Site 2 or Site 8 camps, which together have 205,000 residents, constituting 68% of the total population of the eight camps. The Site 2 and Site 8 Camps are the camps located closest to Khao-I-Dang Hospital and are less than one hour from Khao-I-Dang by ambulance. Based upon the 1990 census data of these camps, the yearly incidence of empyema was 0.37 case per 1,000 children less than 15 years of age. The incidence rate among children 0–4 years of age, 0.47 per 1,000 per year, was significantly higher than the rate for children 5–14 years of age, 0.26 per 1,000 per year ($P = 0.005$). There was no seasonal trend in the incidence of cases. At least one patient with empyema was identified in each of the study months, and the maximum number of patients seen in any study month was 12. The 96 patients referred to Khao-I-Dang hospital with empyema accounted for 3.5% of pediatric referrals during the study period.

The admission characteristics of the 98 patients entered into the study are shown in Table 1. Patients ranged in age from six months to 14 years, with a mean age of 4.1 years (median 3.0 years). Twenty percent of patients were younger than one year, and 34% were older than five years. Most patients were markedly symptomatic when admitted, as judged by a mean respiratory rate of 56/min and the presence of fever in 87% of patients. The mean blood neutrophil count and erythrocyte sedimentation rate were

TABLE 1
Characteristics on admission of 98 children with empyema at Khao-I-Dang Hospital

Patient data	% of patients
Demographic information	
Age (years)	
<2	20
2–4	46
≥5	34
No. of males	69*
Patient history	
Duration of respiratory symptoms (days)	
≤7	56
8–14	21
>14	23
Antimicrobial therapy before admission (days)	
None	12
≤7	74
>7	14
History of family member with tuberculosis	16
History of cough	89
Physical examination findings	
Oral temparture ≥37.5°C	87
Respiratory rate (/min)	
30–49	33
50–69	54
>69	13
Diminished breath sounds on auscultation	85
Dullness to chest percussion	88
Severe malnutrition (weight for age <60% of National Center for Health Statistics median)	17
Laboratory findings†	
Erythrocyte sedimentation rate (mm/hr)	93 ± 34
Blood neutrophil count/mm²	9,490 ± 4,947

* 95% confidence interval 60–78%.
† Values are the mean ± SD.

also markedly elevated. Two children had pyomyositis. No other concurrent major illnesses were noted in the other 96 children.

Evaluation of admission chest radiographs confirmed that most patients had moderate to severe disease (Table 2). Sixty-six percent of the patients had large pleural effusions, 43% had a mediastinal shift, 23% had pneumatoceles, and 21% had a pyopneumothorax. An additional 16% of the patients developed a pyopneumothorax following insertion of the chest tube. Characteristic radiographic findings are illustrated in Figure 1.

TABLE 2
Chest radiograph findings on admission to the hospital

Radiographic finding	% of patients with finding
Site of empyema	
Left pleural space	44
Right pleural space	54
Bilateral	2
Effusion size	
Large	66
Medium	25
Small	9
Mediastinal shift present	43
Pyopneumothorax present	21
Pneumatocele present	23
Pneumonia	97

Chloramphenicol and cloxacillin were the two most commonly prescribed antimicrobial agents, being given to 92% and 72% of the patients, respectively (Table 3). Eight of the 98 patients received one antimicrobial agent on admission, and the remaining 90 received two antimicrobial agents. The most common combination of drugs was chloramphenicol and cloxacillin, given to 68% of patients, followed by chloramphenicol and penicillin, given to 10% of the patients.

All 98 study patients had a chest tube inserted on admission. Twenty-four patients had more than one chest tube, including 17 who had two chest tubes, four who had three chest tubes, and three who had four or more chest tubes. The mean ± SD duration of chest tube drainage was 11.9 ± 9.7 days. Reasons for removing the 132 chest tubes were clinical response satisfactory and further drainage not required, 70 (53%); tube spontaneously dislodged, 23 (17%); and tube not functioning or a loculated effusion, 21 (16%). For 18 (14%) chest tubes the reasons for removal were not recorded.

Forty-two percent of the children five years of age or older had more than one chest tube, compared with 19% of the children younger than five years of age ($P = 0.024$). In older children, the indication for a replacement chest tube in 85% of cases was a loculated pyopneumothorax. In 75% of the children less than five years of age requiring a second chest tube, the second tube was inserted because the previous tube had become spontaneously dislodged. Spontaneous removal of the chest tube was ($P = 0.09$) more common among boys than among girls.

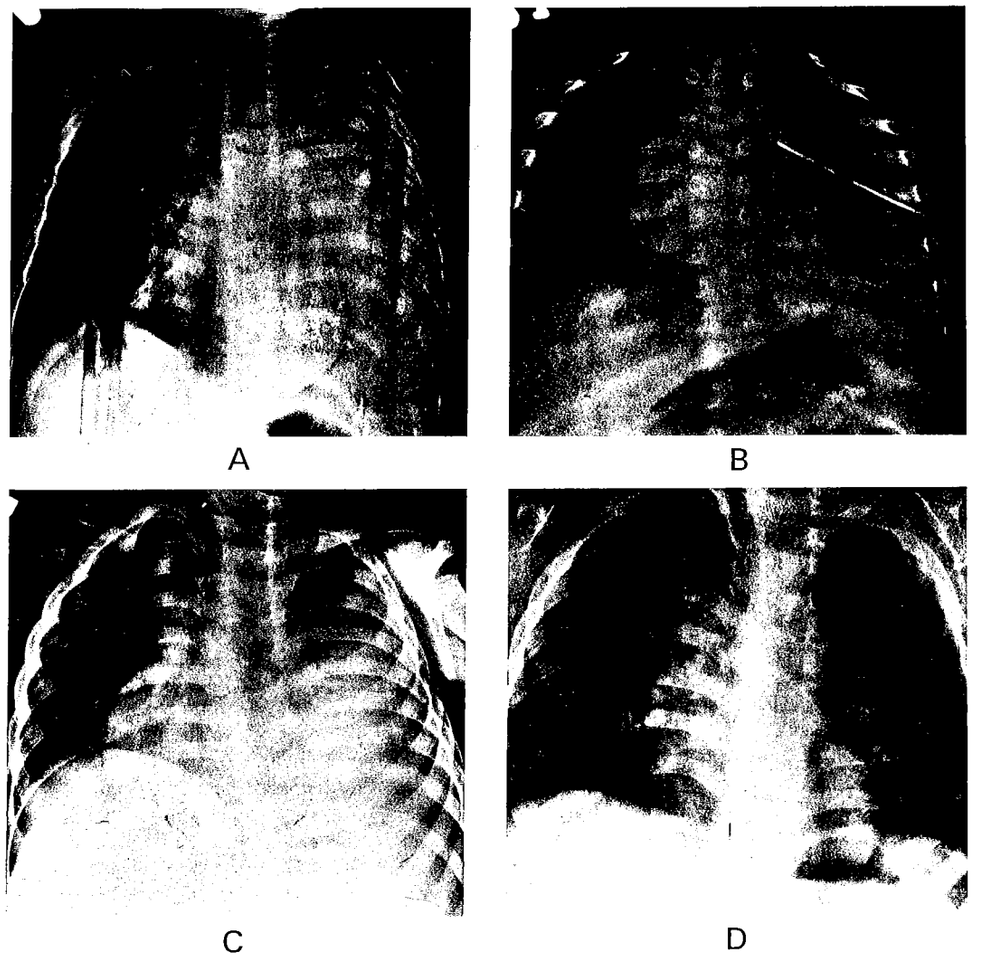

FIGURE 1. Sequential posterior-anterior chest radiographs taken during hospitalization of a 14-month old boy with an 11-day history of cough, fever, and dyspnea. **A,** admission film showing total opacification of the left hemithorax with a mediastinal shift to the right and spreading of ribs on the left. These findings are consistent with a large left empyema. Speckled densities over the lower left lung field are film-processing artifacts. **B,** film taken two days after admission and insertion of a chest tube. There is a left lower lobe consolidation consistent with pneumonitis, residual pleural fluid, and a small amount of air in the pleural space lateral to the lung edge. **C,** film taken on day of discharge, 18 days after the patient was admitted to the hospital and nine days after the chest tube was removed. The patient was afebrile at this time, with a respiratory rate of 48/min. The patient is rotated to the right on this film, which shows partial opacification of the left hemithorax consistent with a moderately large persisting pleural effusion. **D,** film taken at a follow-up visit six months after discharge from the Khao-I-Dang Hospital. The child was asymptomatic at this time. There is no pneumonitis present, and there is minimal pleural thickening along the left lateral lung margin.

Four patients had surgery for persistent bronchopleural fistulas unresponsive to continued chest tube drainage with suction. These four patients were two, four, four, and five years of age, respectively, and had surgery on the 17th, 24th, 30th, and 51st day of hospitalization, respectively. Three (11%) of the 28 patients not treated with cloxacillin required thoracotomy, compared with only (1%) of the 70 patients treated with cloxacillin ($P = 0.07$). Seven patients re-

TABLE 3

Initial antimicrobial regimens provided to 98 patients with empyema at Khao-I-Dang Hospital

Antimicrobial regimen	% of patients who received the regimen
Chloramphenicol and cloxacillin	68
Chloramphenicol and penicillin	10
Chloramphenicol	7
Chloramphenicol and ampicillin	6
Cloxacillin and gentamicin	4
Ampicillin and gentamicin	2
Metronidazole and penicillin	1
Penicillin	1

ceived anti-tuberculous therapy while they were in the hospital. Indications for starting anti-tuberculous drugs in these patients were failure of conventional treatment as evidenced by persistent pleural effusions or pulmonary infiltrates, a history of a family member with tuberculosis, and a positive Mantoux test result. In one patient, the diagnosis of tuberculosis was made from a lymph node biopsy showing characteristic changes.

The mean ± SD duration of hospital stay was 29.7 ± 13.4 days. At the time of discharge, all patients were afebrile and all except one had a respiratory rate less than 50/min. A discharge chest radiograph was available for 79 of the 98 patients. Only three (4%) of these radiographs were normal. Pneumatoceles were present in 22 (28%) patients, and a persistent, small pneumothorax was present in 24 (30%) patients. Opacification in the pleural space, consistent with either a persistent pleural effusion or, more likely, pleural thickening, was present in 76 (96%) patients. In three (4%) patients, the opacity was considered to be large, in 19 (24%) it was medium, and in 54 (68%) it was small. Thirty-five percent of all patients had pneumatoceles and 48% had a pyo-pneumothorax at some point in their stay in the hospital.

No patient died while in the hospital. In the six months following hospital discharge, one patient, a two-year-old boy, died one month after discharge from the Khao-I-Dang Hospital. This child was one of three patients in the study who had a large effusion at discharge from the hospital. In addition, cardiomegaly was present on the discharge chest radiograph. Although he had received six months of anti-tuberculous therapy, including isoniazid, rifampin, streptomycin, and ethambutol before his admission to Khao-I-Dang Hospital, he was restarted on anti-tuberculous therapy one month after his admission to the hospital. No other patient died in the six months following discharge, and no patient was referred back to Khao-I-Dang Hospital for pulmonary problems during this period.

Twenty-five (26%) of the 98 patients returned for evaluation to Khao-I-Dang Hospital six months after discharge. Patients who returned for follow-up were less likely to be malnourished than those who did not return for follow-up (0% versus 23%; $P = 0.014$), but the two groups did not otherwise differ. When examined at the follow-up visit, all children were in good health and without respiratory symptoms. Chest radiographs were completely normal in 11 (44%) of these patients, and the remaining 14 (56%) had minimal pleural thickening.

A linear regression model was used to determine admission characteristics predictive of the duration of chest tube drainage. Three admission characteristics, pneumatoceles on the chest radiograph taken on the day of admission, mediastinal shift on admission chest radiograph, and history of a family member with tuberculosis, were independently associated with a longer duration of chest tube insertion (Table 4). The increased duration of chest tube insertion that was associated with these three factors ranged from 4.0 (for family history of tuberculosis) to 6.2 days (for pneumatoceles). Because the effect of age on the duration of chest tube insertion was modified by gender, an interaction term between age and sex was added to the model. Using this interaction term, when compared with boys ≤ five years of age, boys > five years of age had 7.6 more days of chest tube treatment ($P = 0.002$), girls ≤ five years of age had 4.4 more days of chest tube drainage ($P = 0.06$), and girls > five years of age had 0.5 less days of chest tube drainage ($P = 0.91$) (Table 4). Boys > five years of age, the group with the longest duration of chest tube drainage, more often had a weight for age < 60% of the median ($P = 0.009$) and an illness duration of > 14 days before admission ($P = 0.015$) than boys ≤ five years of age.

DISCUSSION

Based upon the number of admissions for empyema to the Khao-I-Dang Hospital, the incidence of empyema among the 137,000 Cambodian children less than 15 years of age living

TABLE 4

*Admission characteristics independently associated with duration of chest tube drainage in a linear regression model**

Admission characteristics	Slope†	95% confidence interval	*P*
Pneumatoceles on chest radiograph	6.15	(1.52, 10.8)	0.01
Mediastinal shift	4.38	(0.79, 7.97)	0.02
Family member with tuberculosis	4.04	(−0.6, 8,70)	0.09
By comparison with males <5 years old‡:			
Males >5 years old	7.56	(2.92, 12.2)	0.002
Females <5 years old	4.40	(−0.2, 9.01)	0.06
Females >5 years old	−0.46	(−8.9, 7.80)	0.91

* $r^2 = 0.32$.
† The slope equals the increased duration, in days, of chest tube drainage for a patient with this risk factor.
‡ The *P* value associated with the interaction term between age and gender was 0.014.

in refugee camps was 0.37 cases per 1,000 children per year. This incidence rate is likely to be quite exact. A complete census of the refugee camps was conducted in 1989, the year this study was initiated, and was updated the following year. Persons resident in the camps cannot travel freely outside of the camps, and there was little or no emigration during the period that the study was conducted. All medical care must be obtained from United Nations' clinics within the camps, and only the Khao-I-Dang Hospital was capable of inserting and maintaining chest tubes.

There are no other population-based estimates of the incidence of empyema that we could identify. There are, however, studies from developing countries that report on the number of patients admitted to hospital for empyema.[6, 14, 16, 19, 22–24] In these studies, patients with empyema accounted for 0.1–2.2% of pediatric admissions.[6, 23] Patients with empyema accounted for 3.5% of all referrals to Khao-I-Dang Hospital during this study. Khao-I-Dang Hospital was, however, primarily a referral hospital, whereas most of the hospitals included in previous studies provided primary care pediatric services.

The proportion of patients with pneumatoceles, 23%, and mediastinal shift, 43%, in this study was higher than has been suggested by the limited information available from previous studies of children with empyema.[6] The proportion of patients with hydropneumothorax, 21%, was similar to that reported in previous studies (10–30%).[6, 7, 19, 22, 24, 25] Other clinical characteristics of the patients in this study are also consistent with findings described in other studies; a large proportion of children less than two years of age,[2, 8, 15, 24, 26] a disproportionate number of boys,[7, 17, 18] and a preponderance of right-sided disease.[7, 8, 17, 19]

The fatality rate of patients enrolled in this study, 1.0%, was lower than in any other previously reported large series of patients with empyema in developing countries. Among 13 previous studies that reported on 50 or more patients,[6–8, 15-20, 24–27] 10 reported fatality rates above 5.0%. One possible explanation for the low mortality rate in patients in this study was the ready availability of primary health care services in the refugee camps. The availability of such services may have accounted for a low prevalence of illnesses other than empyema in the children enrolled in this study. The efficacy of the referral system, with most children seen at the other camps being able to be transported to the Khao-I-Dong Hospital in less than one hour, may also have contributed to the low mortality rate. Another factor possibly contributing to the low mortality rate in patients in this study was the insertion of a chest tube in all patients on admission to the hospital, unlike some other studies, in which chest tubes were not routinely inserted.

The low mortality rate in this series was achieved despite the absence of diagnostic microbiologic facilities. The high proportion of patients with pneumatoceles in this series suggests that *S. aureus* was a common pathogen, as has been found in studies of empyema that included microbiologic diagnosis.[14, 17, 19, 28] Although most strains of *S. aureus* remain susceptible to chloramphenicol,[29] the results of this study are consistent with recommendations that semisynthetic penicillins should be included in the antimicrobial regimen provided to patients with

empyema in whom invasive *S. aureus* disease is suspected. Indeed, three of the four patients requiring surgery in this series had not initially received cloxacillin, although they had received chloramphenicol. The semisynthetic penicillins are also active against *Streptococcus pneumoniae* and *Streptococcus pyogenes,* two other commonly identified pathogens in patients with empyema. These agents usually lack activity against *H. influenzae;* however, this pathogen has not been a commonly identified cause of empyema in previous studies from developing countries.[14, 17, 19]

Biochemical analysis of the pleural fluid was also not available. Biochemical characteristics of pleural fluid are not, however, a major determinant of the management of patients with empyema.[30] It is unlikely that management of these patients was affected by their absence.

The majority of the patients enrolled in this study had markedly abnormal chest radiographs at the time that they were discharged from the hospital. Despite this, only one patient died in the six months following discharge, and the chest radiographs of all 25 patients who were re-examined six months after discharge were essentially normal. Thus, the criteria used to determine when chest tube drainage should be stopped, and when patients could be discharged from hospital, which were based upon functional, rather than radiographic criteria, appear to have been appropriate.

Deciding when to start anti-tuberculous therapy was difficult. A definitive diagnosis of tuberculosis was made in only one of the seven patients started on anti-tuberculous therapy while in the hospital. The standard screening test for tuberculosis in children, the Mantoux test, has poor sensitivity and specificity in communities, such as these Khmer camps, where a large proportion of the population has been immunized with BCG, or where malnutrition is prevalent, because malnutrition may render the results of this test to be falsely negative. Patient outcome in this study was excellent despite the infrequent use of anti-tuberculous therapy, suggesting that even in communities such as these refugee camps, where tuberculosis is known to be endemic,[31] standard bacterial pathogens account for the vast majority of empyemas in children.

Restricting the use of open thoracotomy and decortication to patients with persistent bronchopleural fistula and accompanying lung collapse appears to have been appropriate, since 93 of the 94 patients without these complications who were provided medical therapy were clinically cured. The one patient who did fail to respond to therapy, and who ultimately died three months after therapy was initiated, appeared to have died from complications of tuberculosis. The rate of success of medical therapy in this study was similar to that of two other studies that also limited the use of thoracotomy,[16, 32] although in neither of those two studies was the rate of open thoracotomy as low as in this study.

In contrast to many previous studies,[16, 20, 25] no patient required a thoracotomy because of a loculated empyema and persistent clinical symptoms. The absence of loculated empyemas in patients in this study may be due to the routine use of chest tubes on admission to the hospital, and the provision of broad spectrum intravenous antimicrobial therapy. In addition, it was difficult to distinguish pleural thickening from persistence of an empyema on chest radiographs. Patients with persistent pleural-based infiltrates were treated on the assumption that they had pleural thickening (especially if they were improving clinically), rather than a persistent empyema.

Other studies have recommended a thoracotomy be routinely performed in all patients moderately or severely ill with an empyema in the belief that it reduces the risk of developing restrictive lung disease.[33, 34] The risk of restrictive lung disease following empyema has not been well established, though it appears to be very low. No tests of pulmonary function were performed on patients in this study, and thus we cannot determine if any of the 25 patients who returned for follow-up examination had pulmonary function abnormalities. However, none had obvious symptoms of pulmonary disease. It is also possible that a more aggressive surgical approach might have shortened the mean duration of hospital stay of 30 days, which was longer than in many previously reported series.[17, 19, 24, 35] Given the potential hazards of thoracotomy, however, especially in developing countries, and the ultimate success of medical therapy in almost all of the study patients, the limited indications for thoracotomy used in this study appear justified.

Of the four factors predictive of duration of chest tube drainage in a linear regression model, the most surprising was age, and how the effect of age differed according to gender. In most reported series of children with empyema, younger age is associated with increased severity of disease, or increased risk of death.[6, 19, 23, 24] In this series, however, younger children had a shorter duration of chest tube drainage, and were more likely to have only a single chest tube, findings similar to those reported from India by Padmini and others.[6] The shorter duration of chest tube drainage in boys ≤ five years of age, when compared with boys > five years of age ($P = 0.002$) and by comparison with girls the same age ($P = 0.06$), may be explained in part by their inclination to pull out their own chest tubes.

In summary, the long-term outcome in patients in this series was excellent despite the absence of diagnostic microbiologic facilities, the very limited use of thoracotomy, and the markedly abnormal chest radiographs that patients had on discharge from hospital. The use of a conservative medical approach that includes the administration of parenteral antimicrobial agents including cloxacillin or a similar semisynthetic penicillin and chloramphenicol, along with closed chest-tube drainage, is a cost-effective means of managing this still common medical problem.

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INCREASED IN VIVO ACTIVATION OF NEUTROPHILS AND COMPLEMENT IN SICKLE CELL DISEASE

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Abstract. Eight patients with homozygous sickle cell anemia, 15 heterozygotes, and eight control individuals were investigated with respect to plasma concentrations of the inflammatory markers lysozyme and myeloperoxidase and the complement activation marker C3d. The patients showed significantly increased levels of myeloperoxidase and C3d, but not lysozyme, compared with the heterozygotes and the controls. The heterozygotes were also significantly different from the controls with regard to C3d concentration. The concentrations of myeloperoxidase and C3d in plasma showed a significant inverse correlation with the hemoglobin concentration. Myeloperoxidase and C3d showed a significant positive correlation. This suggests a role for the neutrophil and the complement system in the pathophysiology of sickle cell disease.

Sickle cell anemia is a hemoglobinopathy caused by a point mutation resulting in an amino acid substitution in the β chain of human hemoglobin. This leads to the characteristic gelation of the hemoglobin under hypoxic conditions and produces the sickled shape of the erythrocyte.[1] Individuals with this disease have three common features: vaso-occlusive phenomena leading to the known painful crisis, hemolytic anemia,[1] and increased susceptibility to bacterial infections.[2] Although some investigators have reported defects in the complement system as the cause for the increased susceptibility to infections,[3, 4] others have not found such defects.[5, 6] Phagocytic functions have been reported to be defective in the monocytes from patients with this disease[7, 8] and impaired migration of the neutrophils has also been reported.[8]

Individuals with the heterozygous form of the sickle cell trait are not affected by sickling unless they are exposed to extremely anoxic conditions and exhibit none of the features described above. People with the sickle cell trait who are infected with *Plasmodium falciparum* have a selective advantage (resistance) compared with those who do not have this trait. This resistance to malaria is not completely understood but likely involved premature sickling and destruction of the parasitized red blood cell due to abnormal properties of sickle cell hemoglobin.[9]

Neutrophil granulocytes form a first line of defense against invading organisms. They are armed with several lytic enzymes in their primary and secondary granules.[10] Myeloperoxidase (MPO), a basic enzyme containing a heme-like molecule,[11] represents a potent killer of organisms, and is present in the primary granules of the neutrophils.[12] Its function has been ascribed to the capacity to produce reactive oxygen radicals.[13] When measured in serum/plasma, MPO is a marker for neutrophil activation.[14] Lysozyme is formed in the primary and secondary granules of human neutrophils and also in monocyte/macrophages and glandular cells. When measured in serum/plasma, lysozyme serves as a macrophage marker.[15]

The measurement of these and other proteins has formed the basis for the new trend in inflammatory process investigations. Their presence in excessive quantities in serum/plasma marks the respective cell activation.

It has been reported that intravascular hemolysis accounts for the destruction of one-third of the sickled erythrocytes, while two-thirds are removed by macrophages in the spleen and other locations.[16] The hemolytic process in sickle cell anemia may involve several components, including activation of complement, macrophages, and neutrophils. Thus, the objective of this preliminary study was to investigate the role of these components in the hemolytic process of sickle cell anemia by measuring the markers of activation of complement, macrophages, and neutrophils in the plasma of homozygous individ-