ORIGINAL ARTICLE

Complicated parapneumonic effusion and empyema thoracis: microbiology and predictors of adverse outcomes

CME

KY Tsang 曾祈殷
WS Leung 梁華盛
Veronica L Chan 陳　利
Alsa WL Lin 連娃妮
CM Chu 朱頌明

Objectives To describe the microbiological characteristics of a cohort of patients with complicated parapneumonic effusion and empyema thoracis, and to identify the potential risk factors for adverse outcomes, with particular reference to the choice of empirical antibiotics, intrapleural fibrinolytics, adherence to management guidelines, and input from pulmonologists.

Design Retrospective review.

Setting Regional hospital, Hong Kong.

Patients All patients with a diagnosis of complicated parapneumonic effusion/empyema thoracis admitted between January 2003 and June 2005.

Main outcome measures Microbiological characteristics, mortality, and surgery-free survival.

Results There were 63 patients, with a mean age of 64 (standard deviation, 16) years and a male-to-female ratio of 45:18. The pleural fluid culture positivity rate was 68%; *Streptococcus milleri* (19%), *Bacteroides* (14%), *Klebsiella pneumoniae* (12%), and *Peptostreptococcus* (7%) were the most common organisms. Thirteen (21%) patients died during their index admission. Use of intrapleural fibrinolytics according to the guideline was associated with survival (P=0.001) while discordant initial antibiotic use was associated with mortality (P=0.002). Discordant initial antibiotic use was also independently associated with reduced surgery-free survival (P<0.001). Subgroup analysis showed that early intrapleural fibrinolytic use (within 4 days of diagnosis) was associated with decreased mortality (P<0.001), increased surgery-free survival (P=0.005), and shorter hospital stay (P=0.039).

Conclusion Organisms identified from complicated parapneumonic effusion and empyema thoracis differ from those giving rise to community-acquired pneumonia. In these patients, adherence to guidelines, early concordant antibiotic treatment, intrapleural fibrinolytics, and input from a pulmonologist were associated with improved outcomes.

Key words
Empyema, pleural; Fibrinolytic agents; Guidelines; Pleural effusion; Pneumonia; Thoracic cavity

Hong Kong Med J 2007;13:178-86

Department of Medicine and Geriatrics, United Christian Hospital, Kwun Tong, Hong Kong:
Division of Infectious Disease
KY Tsang, MB, ChB, MRCP
Division of Respiratory Medicine
WS Leung, MB, ChB, FHKAM (Medicine)
VL Chan, MB, ChB, FHKAM (Medicine)
AWL Lin, RN
CM Chu, MD, FRCP

Correspondence to: Dr CM Chu
E-mail: chucm@ha.org.hk

Introduction

Community-acquired pneumonia (CAP) is a common and serious illness with high morbidity and mortality, as approximately 20% of episodes result in hospitalisation. Community-acquired pneumonia can be a source of both morbidity and mortality, particularly in patients who are hospitalised.[1,2] In a review article, mortality rates from CAP were reported as 5.1% for patients treated either as out-patients or in hospital and 36.5% for those admitted to intensive care units.[3] Pneumonia is the third leading cause of death in Hong Kong.[4] Complicated parapneumonic effusion (CPE) and/or empyema thoracis (ET) complicate pneumonia in 44 to 57% of all pneumonia cases.[5-7] Approximately 15% of patients with parapneumonic effusion die,[8] and in 15 to 40% surgical drainage of the infected pleural space is undertaken.[8,9] The median duration of in-patient care is 15 days, with 20% of patients remaining in the hospital for a month or longer.[8] Most parapneumonic effusions resolve upon use of appropriate antibiotics, but a significant proportion develop CPE/ET that will require drainage with chest tubes, administration of intrapleural

fibrinolytic agents, or surgery. The American College of Chest Physicians (ACCP) has published guideline on the management of parapneumonic effusion based on the best evidence available at the time.[7] The British Thoracic Society (BTS) has also published a similar guideline.[10] Both advocated early drainage of CPE/ET.[7,10] Intrapleural fibrinolytics are considered an acceptable treatment modality in selected patients with CPE/ET, and may be associated with reduced need for surgical drainage and improved outcomes.

Little is known about the bacteriology, antibiotic susceptibility patterns, and outcomes of CPE/ET in local settings. We describe the microbiological characteristics of a cohort of patients with CPE/ET and identify the potential risk factors for adverse outcomes, with particular reference to the choice of empirical antibiotic, use of intrapleural fibrinolytics, adherence to international guidelines, and input from pulmonologists.

複雜性肺炎旁性胸腔積液和膿胸：微生物學特徵與不良後果的預測因子

目的 描述複雜性肺炎旁性胸腔積液和膿胸的微生物學特徵，並從經驗性抗生素、胸腔內纖維蛋白溶解藥、醫療指引的依循以及呼吸內科專家的參與四方面，識別可能引致不良後果的危險因素。

設計 回顧研究。

安排 分區醫院，香港。

患者 2003年1月至2005年6月入院、並診斷患上複雜性肺炎旁性胸腔積液和膿胸的病人。

主要結果測量 微生物學特徵、死亡率、病人無需接受手術而生存的機會。

結果 研究對象共63位病人，平均年齡64歲（標準差：16歲），男女比率為45：18。胸膜液培養陽性率68%，其中米勒鏈球菌（19%）、桿菌（14%）、克雷伯菌（12%）、消化鏈球菌（7%）為最常見的微生物。在入院過程中，有13人（21%）死亡。按醫療指引使用胸腔內纖維蛋白溶解藥與病人生存有明顯關係（P=0.001），最初不當使用抗生素不但引致病人死亡（P=0.002），它本身也會減低病人無需接受手術而生存的機會（P<0.001）。分組分析顯示，及早使用胸腔內纖維蛋白溶解藥（診斷後4天內），可減低死亡率（P<0.001），提高無需手術而生存的機會（P=0.005），縮短留院時間（P=0.039）。

結論 複雜性肺炎旁性胸腔積液和膿胸的微生物與造成社區感染肺炎的微生物不同。在本研究中，假如能遵照醫療指引，及早適當使用抗生素和纖維蛋白溶解藥，並有呼吸內科專家參與，能提升治療效果。

Methods

Study design

This was a retrospective review of the case notes of all in-patients treated for community-acquired CPE/ET in the United Christian Hospital, from January 2003 to June 2005. The United Christian Hospital is a regional hospital with 1335 acute beds, which serves a population of approximately 650 000 in Hong Kong. Based on a discharge diagnosis of pleural effusion, parapneumonic effusion or ET, a list of patients was generated from a computerised clinical management system. To ensure completeness of data collection, the list was cross-referenced with the requests registered in the computerised database in the microbiology laboratory for pleural fluid culture, and a computerised database of the pharmacy recording the use of intrapleural fibrinolytics (urokinase [UK] or streptokinase [SK]) during the same period. Patients were included in this study if they belonged to CPE/ET categories 3 or 4 according to ACCP classification (Table 1).[7]

Data collection

Clinical, laboratory, radiological, and microbiological data of each patient were abstracted using a standard data sheet. Clinical data included demographic information, premorbid illnesses and treatment, Charlson comorbidity index,[11] clinical presentation at the index admission, and acute physiology and chronic health evaluation (APACHE) II score.[12] Treatment data included the types of antibiotics used, chest drainage, use of intrapleural fibrinolytics, and surgical procedures. Intrapleural

TABLE 1. American College of Chest Physicians classification of parapneumonic effusions[7]

Pleural space anatomy	Pleural fluid bacteriology	Pleural fluid chemistry	Category	Risk of poor outcome	Drainage	Additional fibrinolytic, VATS* or surgery required
Minimal, free-flowing effusion (<10 mm on lateral decubitus chest X-ray)	Culture and Gram stain results unknown	pH unknown	1	Very low	No	No
Small-to-moderate free-flowing effusion (>10 mm and <1/2 hemithorax)	Negative culture and Gram stain	pH≥7.2	2	Low	No	No
Large, free-flowing effusion (≥1/2 hemithorax), loculated effusion or effusion with thickened pleura	Positive culture or Gram stain	pH<7.2	3	Moderate	Yes	Yes
	Pus		4	High	Yes	Yes

* VATS denotes video-assisted thoracoscopic surgery

fibrinolytic therapy consisted of UK (Urokinase-Yoshitomi; Mitsubishi Pharma, Osaka, Japan) 100 000 IU daily dissolved in 100 mL normal saline given for 3 days. The specialties of the attending physicians were recorded. Antimicrobial susceptibility testing was performed using disk diffusion according to the Clinical Laboratory Standards Institute.[13]

Outcome measures

The outcomes studied were the (1) number of patients who died within 100 days of admission and (2) number of patients subjected to surgical drainage of the infected pleural fluid within 100 days of admission. The attending physician referred patients for surgery if there was incomplete drainage and persistent sepsis. We analysed potential factors that might be associated with a variety of poor outcomes.

Definition of terms

Management of CPE/ET was considered to conform to ACCP guidelines if drainage with chest tube, together with intrapleural fibrinolytic therapy and/or surgery had been undertaken (Table 1).[7] Attending physicians were categorised into certified pulmonologists (Fellows in Respiratory Medicine of the Hong Kong Academy of Medicine [HKAM]) and non-pulmonologists (mostly Fellows in Advanced Internal Medicine of HKAM). Empirical antibiotic treatment was regarded as 'concordant' if the organism(s) appeared 'sensitive' according to in-vitro susceptibility testing of culture-positive specimens. Antibiotic therapy to which the organism(s) were 'resistant' was considered 'discordant'.

Statistical analysis

Data were expressed as means with standard deviation or medians with interquartile range [IQR] as appropriate unless otherwise specified. The Chi squared test or Fisher's exact test were used to compare categorical variables. Student's *t* test or the Mann-Whitney *U* test were used to compare continuous variables. Times to occurrences of the various outcomes were analysed by life-table analysis and Kaplan-Meier plots. Potential risk factors associated with poor outcomes were analysed by the log-rank test or Cox's regression, where appropriate. A two-tailed P value of <0.05 was considered statistically significant. All analyses were performed with the Statistical Package for the Social Sciences (Windows version 10.0; SPSS Inc, Chicago, [IL], US).

Results

Between 1 January 2003 and 30 June 2005, 80 patients were identified from the computerised clinical management system by diagnostic coding, and eight more were identified by the computerised database from the microbiology laboratory. Records of seven patients were not available for review, 18 patients were excluded (in 10 of them a pleural effusion was not substantiated, and eight pleural fluid results did not fulfil our inclusion criteria), leaving 63 eligible patients for evaluation.

Demographic and clinical characteristics

The demographic and clinical characteristics of the study group are listed in Table 2.

Microbiology results

Of the 63 patients, 43 (68%) had pleural fluid samples that were culture positive, 57 organisms were isolated as some samples grew more than one type of organism. Aerobic Gram-positive, aerobic Gram-negative, and anaerobic bacteria accounted for 39%, 32%, and 30% of organisms respectively. The most commonly isolated bacteria were *Streptococcus milleri* (19%), *Bacteroides* (14%), *Klebsiella pneumoniae* (12%), and *Peptostreptococcus* species (7%). Details of bacteriology and the in-vitro susceptibility pattern to different antibiotics are listed in Table 3. Both amoxicillin/calvulanic acid and ampicillin/sulbactam had good coverage for Gram-positive organisms (86%), but poor coverage for Gram-negative organisms (62%), while cefoperazone/sulbactam had reasonable coverage for Gram-positive organisms (75%) and good coverage for Gram-negative organisms (93%). Carbapenem group had good coverage for both Gram-positive and -negative organisms (89% and 97%). However, fluoroquinolone and cephalosporin (excluding cefoperazone/sulbactam) had poor coverage for the organisms in our cohort.

Treatment profile, adherence to treatment guidelines, and characteristics of attending physicians

All patients received intravenous antibiotics consistent with the American Thoracic Society (ATS) guideline for CAP. The initial choice of empirical antibiotic was: β-lactam/β-lactamase inhibitors (67%), cephalosporins (27%), carbapenem (3%), and fluoroquinolone (3%). The details of individual empirical antibiotic are listed in Table 4. Regarding the 43 (68%) patients in whom the pathogen was identified, initial antibiotic treatment was concordant in 28 (44%), whilst it was discordant in 15 (24%). In the latter patients, the median interval before changing to effective antibiotics was 6 (IQR, 1-9) days.

Eight (13%) of the 63 patients received antibiotics alone; 16 (25%) received antibiotics and chest tube drainage; 39 (62%) received intrapleural fibrinolytic therapy after chest drainage, consistent with international guidelines. A total of seven (11%) of the patients underwent thoracotomy with decortication, because of uncontrolled sepsis and inadequate drainage. The median size of chest drain used was 12 (IQR, 12-22) Fr.

TABLE 2. Baseline demographic and clinical characteristics

Characteristic	Data*
Basic demographic data	
Sex (M/F)	45/18
Mean age (SD) [years]	64 (16)
Smoking status	
Current smoker	18 (29%)
Ex-smoker	21 (33%)
Non-smoker	24 (38%)
Past medical illness	
Cardiovascular disease	24 (38%)
Diabetes mellitus	19 (30%)
Malignancy	16 (25%)
Cerebrovascular disease	10 (16%)
Neurological disease	8 (13%)
Renal disease	8 (13%)
Chronic obstructive pulmonary disease	7 (11%)
Median Charlson comorbidity score (IQR)	1 (0-3)
Clinical presentation of present episode	
Mean duration of symptoms (SD) [days]	5.3 (9.3)
Fever	53 (84%)
Dyspnoea	44 (70%)
Cough	49 (78%)
Sputum production	30 (48%)
Chest pain	44 (70%)
Haemoptysis	3 (5%)
Weight loss	5 (8%)
Mean acute physiology and chronic health evaluation II score (SD)	12.2 (5.4)
Pleural fluid analysis	
Visible purulent fluid	55 (87%)
Mean pH (SD)	6.8 (0.5)
Mean lactic dehydrogenase (SD) [IU/L]	6747 (12 492)
Mean total white cell count (SD) [/mm^3]	107 537 (406 163)
Mean neutrophil count (SD) [%]	92.7 (7.0)
Septations on ultrasonography	43 (68%)
American College of Chest Physicians category	
Class 3	8 (13%)
Class 4	55 (87%)

* **Data are given in numbers with percentages in brackets, unless otherwise specified**

Fifty-two (83%) patients were managed by pulmonologists and the remaining 11 (17%) by non-pulmonologists. There was no difference in terms of ACCP categories managed by the two groups. Pulmonologists were more likely to give intrapleural fibrinolytics (73%) than non-pulmonologists (9%) [P<0.001]. There was no difference in terms of initial antibiotic concordance between patients treated by either group.

Outcome measures

Survival

The 100-day survival was 79%, and all the deaths were in-patients with CPE/ET. With univariate analysis, the use of intrapleural UK according to guidelines was associated with improved survival (P=0.001, Fig a). Whilst older age (P=0.024), a Charlson comorbidity score of >1 (P=0.041),

TABLE 3. Pleural fluid microbiology

Finding	No.	
Patients with culture-positive pleural fluid	43/63 (68%)	
Patients with polymicrobial culture-positive pleural fluid	12/63 (19%)	
Culture-positive samples growing aerobic Gram-positive bacteria*	22/57 (39%)	
Streptococcus milleri	11	
Streptococcus pneumoniae	2	
Streptococcus viridans	2	
Enterococcus species	1	
Methicillin sensitive *Staphylococcus aureus*	3	
Methicillin resistant *Staphylococcus aureus*	1	
Bacillus cereus†	2	
Aerobic Gram-negative bacteria*	18/57 (32%)	
Klebsiella pneumoniae	7	
Escherichia coli	4	
Pseudomonas aeruginosa	2	
Enterobacter species	1	
Acinetobacter species	1	
Serratia species	1	
Campylobacter foetus	1	
Alcaligenes xylosoxidans	1	
Anaerobic bacteria*	17/57 (30%)	
Bacteroides	8	
Peptostreptococcus	4	
Actinomyces israelii	2	
Eikenella corradens	2	
Eurobacterium species	1	
Antimicrobials to which isolates were susceptible	Gram positive, n=28	Gram negative, n=29
β-lactam/β-lactamase inhibitor		
Amoxicillin/clavulanic acid	24 (86%)	18 (62%)
Ampicillin/sulbactam	24 (86%)	18 (62%)
Cefoperazone/sulbactam	21 (75%)	27 (93%)
Ticarcillin/clavulanic acid	21 (75%)	15 (52%)
Piperacillin/tazobactam	23 (82%)	15 (52%)
Fluoroquinolones		
Levofloxacin	18 (64%)	17 (59%)
Ciprofloxacin	18 (64%)	17 (59%)
Cephalosporins		
Cefuroxime	13 (46%)	9 (31%)
Ceftriaxone	16 (57%)	13 (45%)
Cefotaxime	14 (50%)	15 (52%)
Ceftazidime	13 (46%)	17 (59%)
Cefepime	13 (46%)	16 (55%)
Carbapenem		
Meropenem	25 (89%)	28 (97%)
Imipenem/cilastin	25 (89%)	28 (97%)

* **57 organisms were isolated from 43 patients, as some patients had more than one type of organisms in the pleural fluid**

† ***Bacillus cereus* was considered pathogens in two cases because there was evidence of pleural sepsis; the organisms were also present on direct Gram smear; and it was a pure growth on culture**

TABLE 4. Empirical antibiotic therapy for the 63 patients with parapneumonic effusion

Antibiotic	No. (%)
β-lactam/β-lactamase inhibitors	42 (67)
Amoxicillin/clavulanic acid	25 (40)
Cefoperazone/sulbactam	2 (3)
Ticarcillin/clavulanic acid	5 (8)
Piperacillin/tazobactam	10 (16)
Fluoroquinolone	2 (3)
Levofloxacin	2 (3)
Cephalosporins	17 (27)
Cefuroxime	4 (6)
Ceftriaxone	13 (21)
Carbapenem	2 (3)
Meropenem	2 (3)

a high APACHE II score (P=0.010), attending physician being a non-pulmonologist (P=0.002), and discordant initial antibiotic use (P=0.001) were associated with worse survival (Fig b). The size of the chest drain was not associated with survival (P=0.088). Based on multivariate analysis, the use of intrapleural UK was independently associated with improved survival (hazard ratio, 0.276; 95% confidence interval [CI], 0.110-0.694; P=0.006), whilst discordant initial antibiotics use (hazard ratio, 8.727; 95% CI, 2.286-33.319; P=0.002) was independently associated with worse survival (Table 5).

Surgery-free survival

The 100-day surgery-free survival was 67%. With univariate analysis, a lack of drainage with intrapleural UK treatment according to guidelines (P=0.006), attending physician being a non-pulmonologist (P=0.005), and discordant initial antibiotic use (P<0.001) were associated with worse surgery-free survival. The size of chest drain was not associated with surgery-free survival (P=0.141). Based on multivariate analysis, the only factor independently associated with poor surgery-free survival was discordant initial antibiotic use (hazard ratio, 6.882; 95% CI, 2.559-18.508; P<0.001) [Table 5].

Effects of early intrapleural fibrinolytic use on outcome

To further explore whether the timing of intrapleural fibrinolytic administration was associated with different outcomes, we performed a subgroup analysis in the corresponding 39 patients who received intrapleural UK. The median duration of UK use after the diagnosis of CPE/ET was 4 days. Early intrapleural UK use (≤4 days of the diagnosis) was used in 20 patients and later use (>4 days after diagnosis) in 19. Early intrapleural UK use was associated with a lower mortality (P<0.001) [Fig c], increase in surgery-free survival (P=0.005), and shorter hospital stay (P=0.039).

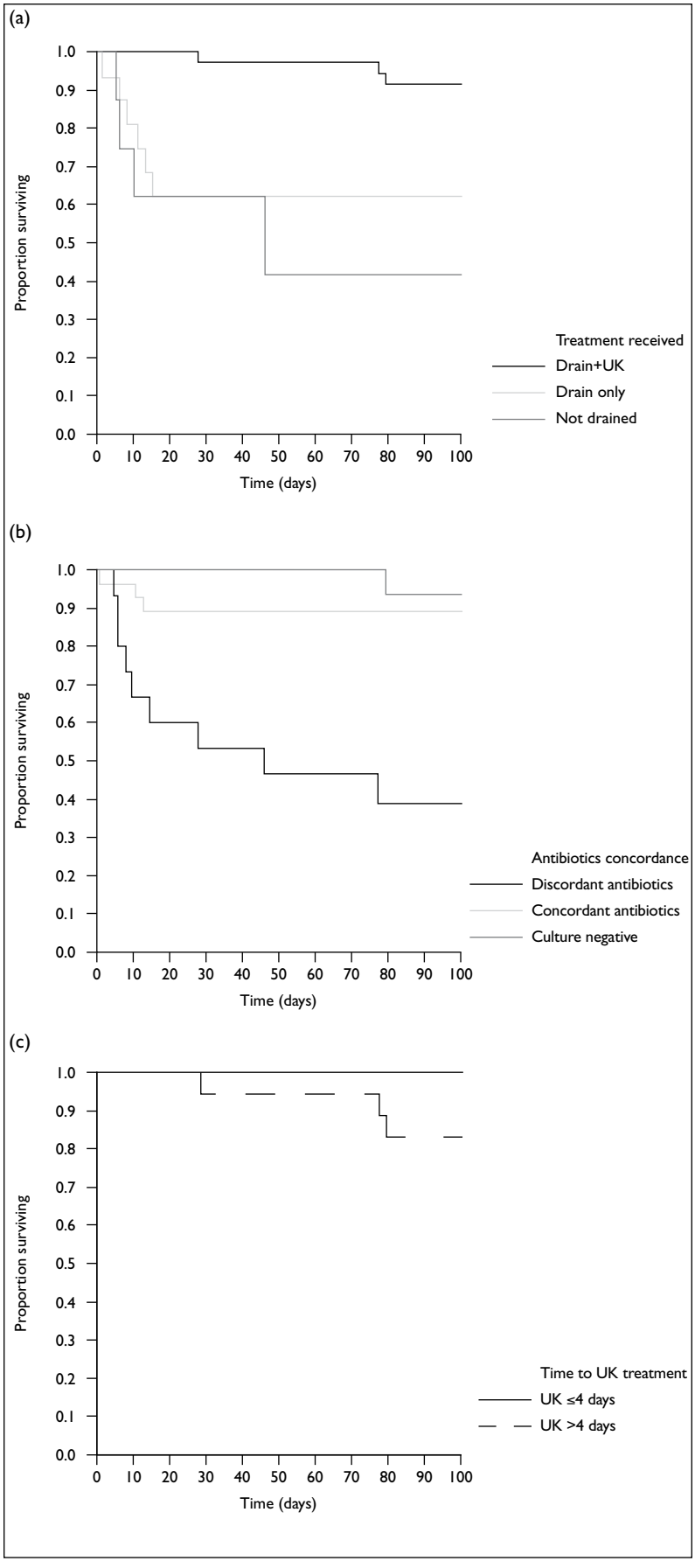

FIG. Survival curves with respect to (a) treatment received (UK=intrapleural urokinase), (b) antibiotics concordance, and (c) time to UK treatment

TABLE 5. Risk factors for mortality and surgery-free survival

Risk factors	Crude hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
For mortality				
Age (per 10 years' increment)	1.541 (1.058-2.244)	0.024	-	-
Female gender	0.454 (0.153-1.353)	0.156	-	-
Charlson comorbidity score (>1)	3.841 (1.057-13.960)	0.041	-	-
Acute physiology and chronic health evaluation II score (per 5 points increment)	2.137 (1.202-3.798)	0.010	-	-
Treatment received	-	0.006	-	0.026
Antibiotic alone	1.0		1.0	
Antibiotic+chest drainage	0.629 (0.177-2.238)	0.474	0.641 (0.147-2.178)	0.576
Antibiotic+chest drainage+urokinase	0.119 (0.032-0.441)	0.001	0.159 (0.046-0.778)	0.007
Attended by pulmonologist	0.166 (0.054-0.504)	0.002	-	-
Antibiotics concordance	-	0.001	-	0.004
Culture negative	1.0		1.0	
Culture positive and concordant therapy	2.290 (0.238-22.020)	0.473	1.918 (0.196-18.756)	0.576
Culture positive and discordant therapy	11.260 (3.030-41.880)	<0.001	8.727 (2.286-33.319)	0.002
For surgery-free survival				
Treatment received	-	0.022	-	
Antibiotic alone	1.0	-	-	-
Antibiotic+chest drainage	0.880 (0.264-2.930)	0.835	-	-
Antibiotic+chest drainage+urokinase	0.276 (0.110-0.694)	0.006	-	-
Attended by pulmonologist	0.264 (0.104-0.669)	0.005	-	-
Antibiotics concordance	-	0.001	-	0.001
Culture negative	1.0	-	1.0	
Culture positive and concordant therapy	2.738 (0.569-13.182)	0.209	2.738 (0.569-13.182)	0.209
Culture positive and discordant therapy	6.882 (2.559-18.508)	<0.001	6.882 (2.559-18.508)	<0.001

Discussion

Our study revealed two important findings. First, adherence to international treatment guidelines was associated with improved outcomes in CPE/ET and that pulmonologists are more likely to adhere to such guidelines than non-pulmonologists. Second, the organisms identified in CPE/ET differ from the usual pathogens causing CAP, and discordant antibiotics use is associated with worse outcomes in terms of the need for surgery and mortality.

In a study on adherence to guidelines for the treatment of CAP, 81% of pulmonologists versus 67% of other specialists complied (P<0.005).[14] Furthermore, such adherence appeared protective for mortality (odds ratio [OR], 0.55; 95% CI, 0.3-0.9) and for treatment failure (OR, 0.65; 95% CI, 0.5-0.9), even after adjusting for Fine risk class. In the management of CPE/ET, the benefit from input by pulmonologists can be due to early recognition, familiarity with different imaging techniques, early resort to drainage, early use of intrapleural fibrinolytic therapy, and early surgical referral. In the BTS guidelines,[10] it is recommended that a pulmonologist or a thoracic surgeon should be involved in the care of all patients requiring chest drainage for a pleural infection, as in draining the pleural space is probably associated with increased morbidity, longer duration of hospital stay, and possibly increased mortality.

Compared to the large Multicenter Intrapleural Sepsis Trial (MIST) I study,[15] our study encountered a slightly higher mortality (21% vs 14-16%). In our cohort, all deaths were due to CPE/ET, and not malignancy or its complication. Both studies recruited patients based on the same criteria and the patients' ages were similar. However, our cohort had more comorbid illness, namely: cardiovascular disease (38% vs 24-30%), diabetes mellitus (30% vs 14-23%), and malignancy (25%, and not mentioned in the MIST I study). These comorbidities might explain the higher mortality in our cohort. The size of the chest drain deserves mentioning: the median size used by us was 12 Fr, which was similar to that in the MIST I study, but all our drains were inserted under ultrasound guidance.

Our study shows intrapleural fibrinolytics appear to be useful, especially when given within the first 4 days of the diagnosis. Its rationale stems from the knowledge that fibrin strands bridge pleural membranes and transform

free-flowing pleural fluid in the early 'exudative' stage of empyema into loculations and fibrous peels in the later 'organised' stage. When intrapleural fibrinolytic agents are given at the early stage, before organisation occurs they are believed to disrupt fibrin loculations, enhance drainage, and obviate the need for surgical drainage.[16,17] Small trials[18-22] and case series[23] support these assertions in that these agents do improve drainage of pleural fluid and may reduce the need for surgery,[21] with few adverse effects. However, these inferences were not supported in a recent MIST I group trial,[15] in which 454 patients with pleural infection were randomly assigned to receive either intrapleural SK (250 000 IU twice daily for 3 days) or placebo. There was no significant difference between the groups with respect to the proportion of patients who died or required surgery (SK, 64/206 [31%] patients vs placebo, 60/221 [27%]; relative risk, 1.14; 95% CI, 0.85-1.54; P=0.43). There was also no benefit of SK in terms of radiographic outcomes or length of hospital stay. However, in an accompanying editorial, Heffner[24] commented that the MIST I study had enrolled a heterogeneous group of patients at all stages of empyema formation. Some patients probably had 'organised' (fibrous) pleural infections and were unlikely to derive benefit from fibrinolysis. We concurred with Heffner[24] and also contended that the lack of benefit could have been due to late administration of the intrapleural fibrinolytic agent. In the MIST I study,[15] the median interval from diagnosis to fibrinolytic use was 14 (IQR, 8-28) days from symptoms onset. Our study suggests that intraplueral fibrinolytic therapy given within 4 days of diagnosis is associated with improved survival and reduced the need for surgery.

Interestingly, adverse outcomes were more frequently associated with discordant antibiotic use. In our study, the pleural fluid culture positivity rate was 68%; the commonest pathogen isolates being *Streptococcus* species (26%), *Bacteroides* (14%), and *Klebsiella pneumoniae* (12%). This study and previous studies have shown that a wide range of aerobic Gram-positive, Gram-negative, and anaerobic organisms are implicated as aetiologic agents in CPE/ET.[15,25-32] *Streptococcus pneumoniae*, the commonest pathogen for CAP was also the commonest pathogen for CPE/ET in the 1960s.[33] However, *Streptococcus pneumoniae* has become a less common aetiologic agent for CPE; other Gram-positive, Gram-negative, and anaerobic organisms are more commonly isolated now. Such a change in pattern may be attributed to the worldwide accessibility of patients to broad-spectrum antibiotics. We postulate that CAP caused by *S pneumoniae* is often treated effectively by antibiotics promulgated by international guidelines[1,2] and that the chance of developing a pleural infection is reduced. The differences in the relative importance of different pathogens in causing CAP and CPE/ET should be appreciated as they have significant treatment implications. Although initial empirical antibiotics consistent with the ATS guideline[1] for CAP were used in all patients in this study, a significant proportion (24%) received discordant antibiotics according to subsequent pleural fluid culture results. Our findings also show that discordant antibiotics treatment is associated with worse outcomes in terms of the need for surgery and mortality.

Our study has several limitations. First, it was retrospective, and prone to missing data. Second, the number of patients was small, which may reduce the statistical power of detecting risk factors with low hazard ratios. Third, it was not a randomised controlled study of intrapleural fibrinolytic therapy in CPE/ET, and so its usefulness cannot be regarded as conclusive. Lastly, computed tomography of the thorax was not performed in all patients.

Conclusion

Adherence to treatment guidelines and concordant initial antibiotic therapy are associated with improved outcomes in CPE/ET patients. Pulmonologists are more likely to adhere to treatment guidelines for CPE/ET and deliver better results. Clinicians should be aware that the bacteriology of CPE/ET is different from that of CAP, and that antibiotics recommended by CAP guidelines may not be adequate in this condition. Further randomised controlled study on the early use of intrapleural fibrinolytics in CPE/ET patients is warranted.

References

1. Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163:1730-54.
2. Mandell LA, Bartlett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003;37:1405-33.
3. File TM. Community-acquired pneumonia. Lancet 2003;362:1991-2001.
4. Death rates for leading causes of death (based on ICD 10th version): 2001 - 2005. HKSAR Centre for Health Protection website: http://www.chp.gov.hk/data153b.html?lang=en&cat=4&dns_sumID=117&id=27&pid=10&ppid=. Accessed 1 Feb 2006.
5. Light RW, Girard WM, Jenkinson SG, George RB. Parapneumonic effusions. Am J Med 1980;69:507-12.

6. Heffner JE, McDonald J, Barbieri C, Klein J. Management of parapneumonic effusions. An analysis of physician practice patterns. Arch Surg 1995;130:433-8.
7. Colice GL, Curtis A, Deslauriers J, et al. Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. Chest 2000;118:1158-71.
8. Davies CW, Kearney SE, Gleeson FV, Davies RJ. Predictors of outcome and long-term survival in patients with pleural infection. Am J Respir Crit Care Med 1999;160:1682-7.
9. Ferguson AD, Prescott RJ, Selkon JB, Watson D, Swinburn CR. The clinical course and management of thoracic empyema. QJM 1996;89:285-9.
10. Davies CW, Gleeson FV, Davies RJ; Pleural Diseases Group, Standards of Care Committee, British Thoracic Society. BTS guidelines for the management of pleural infection. Thorax 2003;58(Suppl 2):18S-28S.
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
13. National Committee of Clinical Laboratory Standards. Performance standards for antimicroibal susceptibility testing: 9th informational supplement. Villanova, PA: National Committed for Clinical Laboratory Standards; 1999.
14. Menendez R, Torres A, Zalacaín R, et al. Guidelines for the treatment of community-acquired pneumonia: predictors of adherence and outcome. Am J Respir Crit Care Med 2005;172:757-62.
15. Maskell NA. Davies CW, Nunn AJ, et al. U.K. controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med 2005;352:865-74.
16. Sahn SA. Use of fibrinolytic agents in the management of complicated parapneumonic effusions and empyemas. Thorax 1998;53(Suppl 2):65S-72S.
17. Idell S, Girard W, Koenig KB, McLarty J, Fair DS. Abnormalities of pathways of fibrin turnover in the human pleural space. Am Rev Respir Dis 1991;144:187-94.
18. Davies RJ, Traill ZC, Gleeson FV. Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection. Thorax 1997;52:416-21.
19. Bouros D, Schiza S, Tzanakis N, Chalkiadakis G, Drositis J, Siafakas N. Intrapleural urokinase versus normal saline in the treatment of complicated parapneumonic effusions and empyema. A randomized, double-blind study. Am J Respir Crit Care Med 1999;159:37-42.
20. Bouros D, Schiza S, Patsourakis G, Chalkiadakis G, Panagou P, Siafakas NM. Intrapleural streptokinase versus urokinase in the treatment of complicated parapneumonic effusions: a prospective, double-blind study. Am J Respir Crit Care Med 1997;155:291-5.
21. Thomson AH, Hull J, Kumar MR, Wallis C, Balfour Lynn IM. Randomised trial of intrapleural urokinase in the treatment of childhood empyema. Thorax 2002;57:343-7.
22. Diacon AH, Theron J, Schuurmans MM, Van de Wal BW, Bolliger CT. Intrapleural streptokinase for empyema and complicated parapneumonic effusions. Am J Respir Crit Care Med 2004;170:49-53.
23. Maskell NA, Davies RJ. Effusions from parapneumonic infection and empyema. In: Light RW, Lee YC, editors. Textbook of pleural diseases. London: Arnold; 2003:310-28.
24. Heffner JE. Multicenter trials of treatment for empyema—after all these years. N Engl J Med 2005;352:926-8.
25. Bhattacharyya N, Umland ET, Kosloske AM. A bacteriologic basis for the evolution and severity of empyema. J Pediatr Surg 1994;29:667-70.
26. Chapman SJ, Davies RJ. Recent advances in parapneumonic effusion and empyema. Curr Opin Pulm Med 2004;10:299-304.
27. Brook I, Frazier EH. Aerobic and anaerobic microbiology of empyema. A retrospective review in two military hospitals. Chest 1993;103:1502-7.
28. Bartlett JG, Gorbach SL, Thadepalli H, Finegold SM. Bacteriology of empyema. Lancet 1974;1:338-40.
29. Wang JL, Chen KY, Fang CT, Hsueh PR, Yang PC, Chang SC. Changing bacteriology of adult community-acquired lung abscess in Taiwan: *Klebsiella pneumoniae* versus anaerobes. Clin Infect Dis 2005;40:915-22.
30. Chen KY, Hsueh PR, Liaw YS, Yang PC, Luh KT. A 10-year experience with bacteriology of acute thoracic empyema: emphasis on *Klebsiella pneumoniae* in patients with diabetes mellitus. Chest 2000;117:1685-9.
31. Eastham KM, Freeman R, Kearns AM, et al. Clinical features, aetiology and outcome of empyema in children in the north east of England. Thorax 2004;59:522-5.
32. Schultz KD, Fan LL, Pinsky J, et al. The changing face of pleural empyemas in children: epidemiology and management. Pediatrics 2004;113:1735-40.
33. Finland M, Barnes MW. Changing ecology of acute bacteria empyema: occurrence and mortality at Boston City Hospital during 12 selected years from 1935 to 1972. J Infect Dis 1978;137:274-91.