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Risk Factors for Complicated Parapneumonic Effusion and Empyema on Presentation to Hospital with Community Acquired Pneumonia

James D Chalmers , Aran Singanayagam, Maeve P Murray, Caroline Scally, Ali Fawzi, Adam T Hill
Royal Infirmary of Edinburgh, Edinburgh, Scotland, United Kingdom.

Corresponding author
Dr James Chalmers
Department of Respiratory Medicine
Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road
Edinburgh
EH16 4SA
E-mail: jamesdchalmers@googlemail.com
Tel: 0131 242 1000

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ABSTRACT

BACKGROUND

The aim of this study was to identify key factors on admission predicting the development of complicated parapneumonic effusion or empyema in patients admitted with community acquired pneumonia.

METHODS

We conducted a prospective observational study of patients admitted with community acquired pneumonia in NHS Lothian, UK. We used multivariate regression analyse to evaluate factors that could predict the development of complicated parapneumonic effusion or empyema including admission demographics, clinical features, laboratory tests, pneumonia specific (PSI, CURB65 and CRB65) and generic sepsis scoring systems (APACHE II, SEWS, SIRS).

RESULTS

1269 patients were included in the study and 92 patients (7.2%) developed complicated parapneumonic effusion or empyema. The pneumonia specific and generic sepsis scoring systems had no value in predicting complicated parapneumonic effusion or empyema.
Multivariate logistic regression identified albumin <30g/L adjusted odds ratio (AOR) 4.55 (95% confidence interval 2.45-8.45,p<0.0001), sodium <130mmol/l AOR 2.70 (1.55-4.70,p=0.0005), platelet count >400×10^9/L AOR 4.09 (2.21-7.54,p<0.0001), C-reactive protein >100mg/l AOR 15.7 (3.69-66.9,p<0.0001) and a history of alcohol abuse AOR 4.28 (1.87-9.82,p=0.0006) or intravenous drug use AOR 2.82 (1.09-7.30,p=0.03) as independently associated with development of complicated parapneumonic effusion or empyema. A history of COPD was associated with decreased risk AOR 0.18 (0.06-0.53,p=0.002).
A 6 point scoring system using these combined variables had good discriminatory value AUC 0.84 (95% confidence interval 0.81-0.86,p<0.0001).

CONCLUSION

This study has identified 7 clinical factors predicting the development of complicated parapneumonic effusion or empyema. Independent validation is needed.

ABSTRACT WORD COUNT – 235 words.

KEYWORDS: Pleural Empyema; Community Acquired Pneumonia; Complicated Parapneumonic Effusion; Severity Scores

INTRODUCTION

Complicated parapneumonic effusions and empyema are key complications of community acquired pneumonia necessitating prolonged treatment, intercostal drainage and frequently surgical management leading to prolonged hospital stay.[1-3]

In 1980 Light and colleagues established the criteria that are now used to define complicated parapneumonic effusions but found no reliable clinical or radiological features to predict which patients with community acquired pneumonia will develop complicated parapneumonic effusions or empyema.[4] Only small studies have been available to date.

Pneumonia severity scores including CURB65, CRB65 and the Pneumonia Severity Index [5-9] have been used on admission to predict 30-day mortality but none to date have studied their utility to predict the development of complicated parapneumonic effusion or empyema.

The aim of this study was to identify key factors predicting the development of complicated parapneumonic effusion or empyema in patients admitted with community acquired pneumonia.

METHODS

We prospectively identified all patients, admitted between January 2005 and January 2008 to NHS Lothian UK, with a primary diagnosis of community acquired pneumonia. Ethical approval was obtained from the Lothian research ethics committee.

The inclusion criteria and study protocol have been described previously.[9] Exclusion criteria were hospital acquired pneumonia (development of symptoms >48 hours after admission to hospital or discharge from an acute care facility within 14 days of admission); active thoracic or extrathoracic malignancy; metastatic infection from a non-pulmonary source; immunosuppression (including patients prescribed long term prednisolone, methotrexate, azathioprine or anti-TNF alpha therapy); solid organ transplant; previous empyema or chronic pleural effusion due to a cause other than pneumonia; recent thoracic surgery; patients for whom active treatment is not considered appropriate (e.g palliative care).

Identification of Parapneumonic Effusions

All patients had a standard chest radiograph within 24 hours of admission and this was repeated if clinically indicated. All patients with pleural effusions underwent clinical assessment and thoracic ultrasound if required. All patients with pleural effusion underwent thoracocentesis, except in small pleural effusions thought unsafe for pleural aspiration from thoracic ultrasound. Fluid was analysed for pH, protein, lactate dehydrogenase, glucose, gram stain, culture and cytology. In patients with empyema too viscous to analyse the sample was sent for gram stain and microbiological culture only.

Definition of Complicated Pneumonia and Empyema

The primary outcome was development of complicated parapneumonic effusion or empyema. Complicated parapneumonic effusion was defined according to the criteria described by Light and colleagues [4] as at least one of pleural fluid pH < 7.2, LDH >1,000iu/l or glucose <2.2mmol/l. Empyema was defined as frank pus aspirated from the pleural space or positive gram stain/culture for pathogenic organisms.

For the purposes of comparison, early development of complicated parapneumonic effusion/empyema was defined as diagnosis $\leq$72 hors after admission to hospital. Late development of empyema was defined as diagnosis >72 hours after admission. The date of diagnosis of empyema was taken to be the date of the confirmatory thoracocentesis.

Severity Scores

We evaluated factors that could predict the development of complicated parapneumonic effusion or empyema including admission demographics, clinical features, laboratory tests, and severity scores. The pneumonia specific scores included the Pneumonia Severity Index[7], CURB65[5] and CRB65[5]. The generic sepsis scores included the APACHE II score[10], SIRS criteria[11] and SEWS (Scottish Early Warning System) Score.[12] For the purposes of calculating the values of predictive tests the following were used to define “severe” for each scoring system, PSI $\geq$ 4; CURB65 $\geq$ 3; CRB65 $\geq$ 3; SIRS -Severe sepsis or Septic shock; SEWS $\geq$ 4; APACHE II- The APACHE score is a progressive scale with increasing estimated death rates for increasing scores. For purposes of comparison in this study “severe”

was arbitrarily set at > 9 points prior to the study which equates to a >9.9% risk of death.

Statistical Analysis

Demographic, clinical, laboratory, radiological and other variables were converted to binary variables based on cut-points identified in the community acquired pneumonia literature, primarily studies focussing on mortality. The relative risks were expressed as adjusted odds ratios (AOR) and 95% confidence intervals (CI). All variables that were statistically significant in the univariate analysis with a P value < 0.05 were entered in a multivariable model with a stepwise approach. Multicollinearity was assessed by using bivariate linear regression between variables and using the variance inflation factor. A variance inflation factor of less than 2.5 was regarded as excluding significant interactions.[13]

The value of tests for predicting outcomes was compared using the area under the receiver operator characteristic curve (AUC).[14] For interpretation of these values the following is widely accepted- AUC 0.50-0.59= no value of test; 0.60-0.69= poor discriminatory value; 0.70-0.79= moderate discriminatory value; 0.80-0.89= good discriminatory value; 0.90-1.00= excellent discriminatory value.

The chi-square ($\chi 2$) test was used to compare categorical variables and for continuous variables the Mann-Whitney U test was used for two groups. Data is presented as number (percentage) or median (interquartile range). A p value of <0.05 was considered statistically significant for each analysis.

RESULTS

1628 patients were considered for inclusion and 359 patients were excluded (see Figure 1). 1269 patients were therefore included in the study. 92 patients (7.2%) met the criteria for complicated parapneumonic effusion (74 patients- 5.8%) or empyema (18 patients- 1.4%).

Figure 1- Method of identification of cases of complicated parapneumonic effusion and empyema.

Baseline characteristics and co-morbidities of the study population are shown in Table 1. Pleural fluid characteristics were as follows for patients developing complicated parapneumonic effusion or empyema: median pH 7.1 (interquartile range 7.0-7.2); glucose 1.0mmol/l (0.6-2.5), Protein 40g/l (35-46); LDH 2900iu/l (1035-4720).

BASELINE CHARACTERISTICS AND CO-MORBIDITIES	Study population	CPE/Emp	Uncomplicated Pneumonia	p-value*
N	1269	92	1177	
Age (years)	66 (51-78)	57 (41-68)	67 (51-78)	<0.0001
Gender (% male)	49.2%	57.6%	48.5%	0.1
Chronic Cardiac Disease	19.1%	9.8%	19.8%	0.02
Liver Disease	5%	10.9%	4.6%	0.009
Neurological Disease	11.1%	2.2%	11.8%	0.01
Chronic Renal Failure	6%	6.5%	5.9%	0.8
Diabetes Mellitus	10.2%	6.5%	10.5%	0.2
COPD	20.3%	4.3%	21.5%	0.0005
Chronic Alcohol Abuse	5.5%	13%	4.9%	0.002
Intravenous Drug Use	3%	10.9%	2.4%	<0.0001
Current Smokers	34.2%	44.6%	33.4%	0.04

Table 1- Baseline characteristics of the study population. (CPE/Emp=complicated parapneumonic effusion or empyema). COPD= Chronic Obstructive Pulmonary Disease. *p-value is derived from comparison between patients with CPE/Emp and patients with uncomplicated pneumonia using the chi-square ($\chi 2$) test except for age (Mann-Whitney U test).

Microbiology of Empyema

16/92 patients had a positive pleural fluid culture. Streptococcus milleri group (*S.intermedius, S.constellatus, S.mitis*) were the most frequent organisms isolated in 6 cases. *Streptococcus pneumoniae* was isolated in 2 cases and other Streptococci were isolated in 4 cases. 2 samples grew anaerobic organisms. *Staphylococcus aureus* and Enterobacteriaceae were isolated in a single case. 92 patients (100%) had received antibiotic therapy prior to pleural aspiration. The organisms isolated are shown in figure 2.

Figure 2- Microbiology of empyema.

Outcomes in patients with and without complicated parapneumonic effusion or empyema

Patients with complicated parapneumonic effusion or empyema had longer length of stay and higher rates of intensive care unit admission compared to patients without these complications. The 30-day mortality rate was not significantly different between groups- table 2.

Outcome	Complicated parapneumonic effusion/ empyema	No complicated parapneumonic effusion/ empyema	p-value
Length of Stay (days)	16 (11-26)	5 (2-10)	<0.0001
Intensive Care Unit Admission	21.7%	7.7%	<0.0001
30-day Mortality	8.7%	8.4%	0.9

Table 2- Outcomes in patients with complicated parapneumonic effusion or empyema. p-values refer to comparisons between patients with and without complicated parapneumonic effusion and empyema using the chi-square ($\chi 2$) test except for length of stay (Mann-Whitney U test).

92 patients (100%) meeting the criteria for complicated parapneumonic effusion or empyema had an intercostal drain inserted for drainage of their effusion. Intrapleural fibrinolytics were not used. 18 patients failed to improve with chest tube drainage and subsequently required surgical thoracotomy. 2 of these patients died within 30-days of admission. A further 6 patients died within 30-days that did not receive thoracotomy. 24 patients (22%) were therefore categorised as failure of medical treatment.

Recognised Severity Scores

Recognised severity scores were compared for their ability to predict the development of complicated parapneumonic effusion or empyema. All had low area under the receiver operator characteristic curves for the prediction of complicated parapneumonic effusion and empyema see figure 3 and Table 3.

The positive predictive value, negative predictive value, sensitivity, specificity and area under the curve for each rule is shown in Table 3.

Prediction Tool	PPV	NPV	Sensitivity	Specificity	AUC (95% CI)	p-value
Pneumonia Severity Index	8.8%	94.2%	57.6%	53.4%	0.55 (0.52-0.58)	0.1
CURB65 Score	7.5%	92.9%	33.7%	67.5%	0.54 (0.51-0.57)	0.2
CRB65 Score	4.4%	92.2%	9.8%	83.5%	0.52 (0.49-0.55)	0.5
APACHE II score	5.7%	90.2%	47.8%	37.7%	0.41 (0.38-0.44)	0.002
SIRS	8.2%	92.9%	15.2%	86.7%	0.57 (0.54-0.60)	0.03
Early Warning Score	7.9%	93.2%	45.7%	58.2%	0.53 (0.50-0.56)	0.3

Table 3- Severity scores and prediction of complicated pneumonia. PPV= positive predictive value; NPV= negative predictive value; AUC= Area under the receiver operator characteristic curve; SIRS= Systemic Inflammatory Response Syndrome. *p-value refers to comparison between ROC curve and the null hypothesis.

Figure 3- Receiver operator characteristic curves for widely used severity scores and development of complicated parapneumonic effusion or empyema.

Prediction of Development of Complicated Parapneumonic Effusion or Empyema

Complete clinical data were available for all patients with the exception of arterial blood gas measurements which were not performed in all patients and so were not included in the multivariate analysis.

On multivariate logistic regression, low serum albumin <30g/l, elevated C-Reactive Protein >100mg/l and platelet Count >400 x 10^9/L, low serum sodium <130mmol/l, intravenous drug use or chronic alcohol abuse were all were identified as independent predictors of the subsequent development of complicated parapneumonic effusion or empyema. A history of chronic obstructive pulmonary disease was associated with decreased risk. (Table 4) No strong correlations were identified between predictors. No VIF was >2.5 and the average VIF was 1.03.

Clinical Feature	N	% CPE/Emp	% Uncomplicated pneumonia	Adjusted Odds Ratio (95% Confidence Intervals)	p-value
Albumin <30g/L	144	38.0%	9.3%	4.55 (2.45-8.45)	<0.0001
C-Reactive Protein >100mg/L	948	97.8%	72.9%	15.7 (3.69-66.9)	0.0002
Platelet Count >400 x 10^9/L	157	31.5%	10.9%	4.09 (2.21-7.54)	<0.0001
Sodium <130mmol/L	105	19.6%	7.4%	2.70 (1.55-4.70)	0.0005
Intravenous Drug Use	38	10.9%	2.4%	2.82 (1.09-7.30)	0.03
Chronic Alcohol Abuse	70	13%	4.9%	4.28 (1.87-9.82)	0.0006
Chronic Obstructive Pulmonary Disease	257	4.3%	21.5%	0.18 (0.06-0.53)	0.002

Table 4- Clinical Predictors of Development of Complicated Parapneumonic Effusion or Empyema- final multivariate model.

Clinical Application of the Data

A scoring system was developed to assess if the identified "risk factors" for development of complicated parapneumonic effusion or empyema could be applied clinically. Each risk factor identified in the multivariate analysis that predicts complicated parapneumonic effusion or empyema (Table 5) was given a numerical value (+1 point). 1 point was subtracted for the presence of COPD. The incidence of complicated parapneumonic effusion or empyema according the number of risk factors is shown in Table 5.

Number of Patients			
Points	CPE/EMP	Uncomplicated Pneumonia	%
-1	0	66	0
0	1	296	0.003
1	11	442	2.4
2	38	283	11.8
3	28	81	25.7
4	12	7	63.2
5	2	2	50*
6	0	0	-

Table 5- Risk stratification using a derived score for prediction of complicated parapneumonic effusion or empyema. *Chi square test, $p<0.0001$.

Although in theory this was a 6 point score, in practice no patients had the maximum of 6 points. The resultant scoring system was analysed using area under the receiver operator characteristic curve. There appeared to be a clear separation between patients with 1 point (2.4%) and patients with higher scores (11.8% and increasing) and so performance characteristics were calculated with these values representing high and low risk of developing complicated parapneumonic effusion and empyema.

For predicting complicated parapneumonic effusion or empyema, using $\geq$2 point as the cut-off, the Sensitivity is 87.0%, specificity is 68.3%, positive predictive value is 17.7%, negative predictive value is 98.5% and Area under the receiver operator characteristic curve is 0.84 (0.81-0.86),$p<0.0001$ (Figure 4). This score was superior to all of severity scores in Table 3 for prediction of complicated parapneumonic effusion or empyema ($p<0.0001$ for all analyses).

Figure 4- Receiver operator characteristic curve for the derived risk score and prediction of complicated parapneumonic effusion or empyema.

Early versus Late Complicated Parapneumonic Effusion/Empyema

22 patients (24%) had the diagnosis of complicated parapneumonic effusion or empyema made within 72 hours of admission. The AUC for the derived score was 0.86 (0.81-0.91) for prediction of early complicated parapneumonic effusion/empyema and the AUC was 0.83 (0.80-0.86) for prediction of late complicated parapneumonic effusion/empyema.

Discussion

This study has identified seven key features that can identify patients at risk of development of complicated parapneumonic effusion or empyema. Low serum albumin <30g/l, C-reactive protein >100mg/l, platelet count >400 x 10^9/L, serum sodium <130mmol/l, intravenous drug use and chronic alcohol abuse were all were identified as independent predictors of the subsequent development of complicated parapneumonic effusion or empyema. A history of chronic obstructive pulmonary disease was found to be associated with decreased risk.

Using this information, this study has provided proof of the concept that complicated parapneumonic effusion and empyema can be predicted by deriving a scoring system with good predictive value. The presence of 2 or more of the above risk factors has a 87% sensitivity for detection of complicated parapneumonic effusion or empyema and a score of <2 gives a negative predictive value of 98.5%. The scoring system had "good" performance characteristics for predicting both early and late parapneumonic effusion and empyema. This scoring system now requires independent validation.

Although in univariate analysis, patients with complicated parapneumonic effusion and empyema were younger, more likely to be male and more likely to be current smokers, these differences were not significant in the multivariate analysis.

The risk factors identified in this study are supported by the existing literature. Alcohol abuse is the most common disorder reported in patients with empyema.[15,16] Aspiration of gastric contents and the failure to seek prompt medical attention are two mechanisms that have been proposed to explain this. This may also in part explained the increased incidence of patients with a history of intravenous drug use. There is strong evidence that inflammatory markers are elevated in patients with parapneumonic effusions and empyema, as pleural inflammation is the characteristic feature of these diseases.[17] In the present study C-Reactive protein >100mg/L was strongly associated with the development of empyema or complicated parapneumonic effusion. It is well recognised that patients with an elevated C-Reactive protein on admission that fails to fall with treatment are at increased risk of complicated parapneumonic effusion or empyema.[18-20] Elevated platelet count is also well recognised in acute and chronic infections.[21] Empyema is a recognised cause of the syndrome of inappropriate ADH secretion[22], but hyponatraemia is also recognised in severe community acquired pneumonia without syndrome of inappropriate ADH.[23] Hypoalbuminaemia is well recognised in severe community acquired pneumonia as well as being associated with the development of empyema.[7,23,24]

The finding that patients with chronic obstructive pulmonary disease was associated with a decreased risk of complicated parapneumonic effusion and empyema is intriguing. There are compelling reasons to believe that patients with COPD should have increased mortality from pneumonia but prognostic studies to date have found that this is not the case.[7,23] Authors have speculated that the local pulmonary inflammation present in patients with COPD may produce a dampened response when exposed to an acute bacterial challenge.[25] The acute administration of steroids is another important potential confounding factor. Steroids have potent effects on attenuating pulmonary and systemic inflammation[26] and may also attenuate pleural inflammation.

The widely used pneumonia severity and sepsis severity scores considered in this study were not found to be useful for predicting the development of complicated parapneumonic effusion or empyema. The clinical features that predispose to 30-day mortality from pneumonia are clearly different to those identified in this study to predispose to the development of complicated parapneumonic effusion or empyema. Of the risk factors identified in this study, only hypoalbuminaemia, hyponatraemia and an elevated C-reactive protein have been identified as independent risk factors for mortality, and none of these are among the "core" high risk features carrying the greatest risk of death.

This study found that *Streptococcus milleri* group was the most frequently isolated organism in patients with empyema, followed by other streptococci. This is consistent with the findings of the UK trial of intrapleural streptokinase and a recent study of patients with community acquired pleural infection from Canada.[27,28] 82% of patients, however, had no organisms cultured. The frequency of positive microbiological diagnosis in this study is lower than in many other published studies of empyema, which have reported a microbiological diagnosis in between 40% and 60% of cases.[29-32] Several factors may account for this, first many of these studies have reported positive blood cultures in addition to positive fluid microbiology[29] rather than simply positive pleural fluid cultures, which it the case in this study. Many studies have focussed exclusively on empyema and consequently reported a much higher incidence of patients with frankly purulent effusions[27-30], which may be more likely to give a positive result. In addition, prior antibiotic therapy is likely to play a role, as empirical therapy in CAP covers the majority of potential organisms, whereas in other studies, the aetiology of empyema is variable and it cannot be said with certainty whether empirical therapy was effective against the organisms isolated.

Limitations

Although the clinical assessment of patients in this study was comprehensive, 27 patients had pleural effusions that were not sampled, because thoracic ultrasound indicated insufficient pleural fluid to tap safely. As all patients were followed up, we feel that it unlikely that clinical important cases of pleural infection were missed.

This study represents a large cohort of patients with community acquired pneumonia, the number developing the outcome of interest (92 patients in total) were relatively small, and this is reflected in the wide confidence intervals for some of the individual predictors. Multicentre studies would be required to define the relative risks more accurately.

Athough the performance of the derived predictive score is defined as "good" (AUC 0.84) in our study population, prospective validation is required before any recommendations can be made about its use in clinical practice.

Conclusion

There are important differences in the presentation of patients with complicated parapneumonic effusion and empyema compared to patients with uncomplicated community acquired pneumonia. Pneumonia and generic sepsis scores do not predict the development of these complications but a simple 6 point scoring system can allow identification of high risk patients. Independent validation studies are needed.

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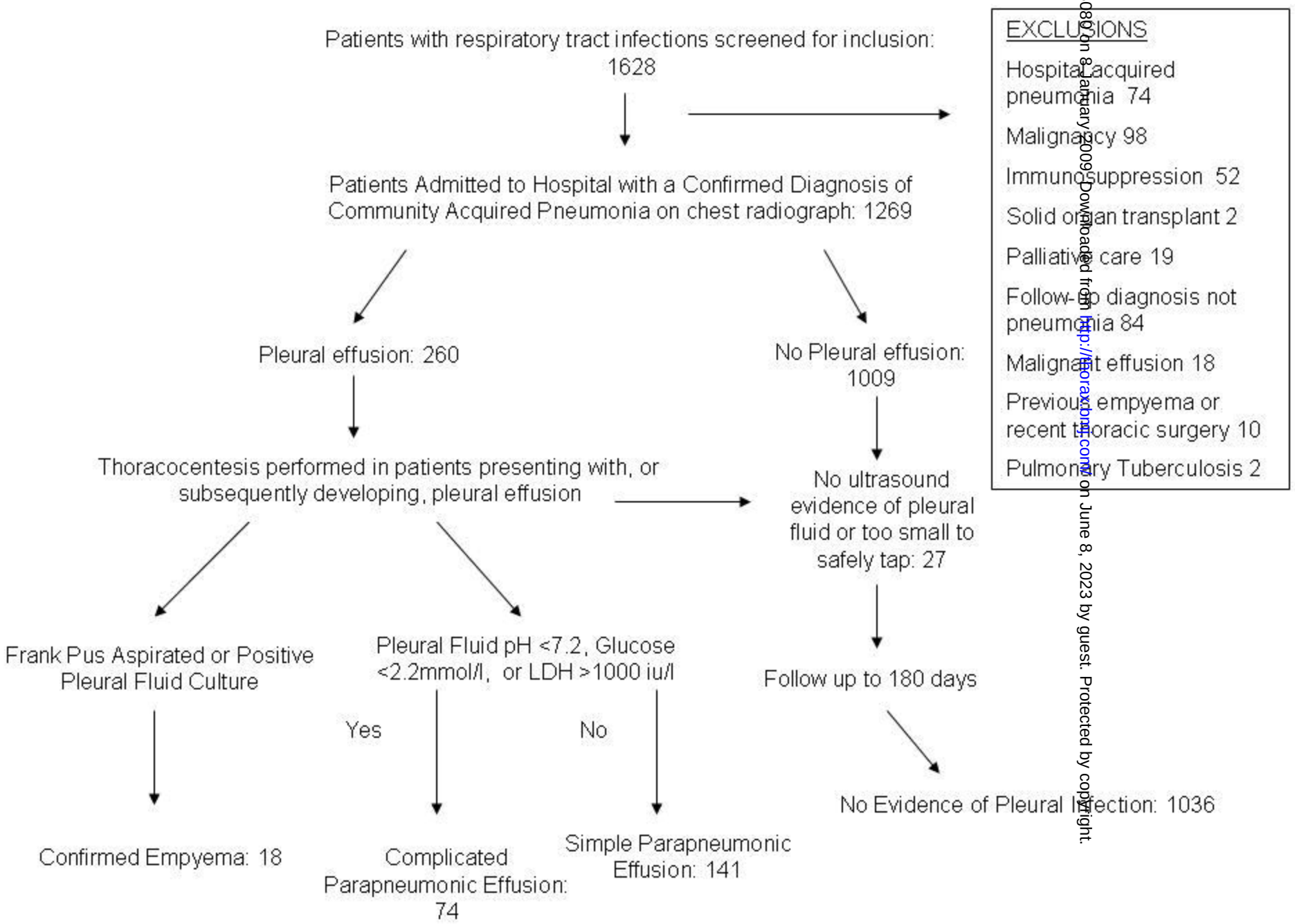

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Microbiology of Empyema