RESPIRATORY INFECTION

Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome

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Background: An inadequate response to initial empirical treatment of community acquired pneumonia (CAP) represents a challenge for clinicians and requires early identification and intervention. A study was undertaken to quantify the incidence of failure of empirical treatment in CAP, to identify risk factors for treatment failure, and to determine the implications of treatment failure on the outcome.

Methods: A prospective multicentre cohort study was performed in 1424 hospitalised patients from 15 hospitals. Early treatment failure (<72 hours), late treatment failure, and in-hospital mortality were recorded.

Results: Treatment failure occurred in 215 patients (15.1%): 134 early failure (62.3%) and 81 late failure (37.7%). The causes were infectious in 86 patients (40%), non-infectious in 34 (15.8%), and undetermined in 95. The independent risk factors associated with treatment failure in a stepwise logistic regression analysis were liver disease, pneumonia risk class, leucopenia, multilobar CAP, pleural effusion, and radiological signs of cavitation. Independent factors associated with a lower risk of treatment failure were influenza vaccination, initial treatment with fluoroquinolones, and chronic obstructive pulmonary disease (COPD). Mortality was significantly higher in patients with treatment failure (25% *v* 2%). Failure of empirical treatment increased the mortality of CAP 11-fold after adjustment for risk class.

Conclusions: Although these findings need to be confirmed by randomised studies, they suggest possible interventions to decrease mortality due to CAP.

The incidence of community acquired pneumonia (CAP) in adults ranges from 5 to 10 per 1000 population with an incidence of 4 million cases a year in the USA.[1] Pneumonia and influenza are the infections causing the largest proportion of deaths, and there has been no reduction in mortality rates associated with these infections in recent decades.[2–4]

Adequate antibiotic treatment and initial severity of CAP (pneumonia severity index (PSI); risk classes of Fine[5]) are factors that determine the outcome of the disease. The incidence of treatment failure in CAP has been estimated to be 11% and the generally accepted period of time considered for failure is 72 hours.[6 7] Progressive pneumonia has been defined as progression of the disease after 72 hours of treatment.[7] However, severe clinical deterioration may appear even earlier and risk factors for this serious development are not well known.

Although many epidemiological and prognostic studies of CAP have been published, there is very little information about treatment failure in CAP. Studies are needed to identify patients and/or risk factors for treatment failure and to design different strategies or plan specific health care and/or treatment for these patients. Moreover, treatment failure increases the need for microbiological and diagnostic tests with the resulting longer hospital stay and increased costs.

Prognostic evaluation scales permit the classification of patients into different grades of risk of mortality,[5] and it is reasonable to assume that, the more severe the CAP, the higher the incidence of failure of empirical treatment. Moreover, older patients and those with chronic diseases receive antibiotic treatment more frequently and therefore have a higher probability of resistant and uncommon microorganisms. However, the degree to which the initial severity and the presence of co-morbid conditions influence the response to initial empirical treatment is unknown.

The aims of this study were to identify factors associated with failure of empirical treatment and to determine the incidence of both early (<72 hours) and late treatment failure and their implication on the outcome. To achieve these objectives the patients were stratified according to initial risk class.

METHODS

Patients

From October 2000 to April 2001 a multicentre observational prospective study was carried out in 15 Spanish hospitals. The study cohort comprised adult patients (>16 years of age) hospitalised with CAP. The inclusion criteria were a clinical picture compatible with CAP, with at least two clinical symptoms and a new radiographic infiltrate. Patients with a previous neoplasm who had not received immunosuppressive treatment during the preceding 6 months and residents in nursing homes were also included. Exclusion criteria included patients admitted within the previous 15 days, the appearance of pneumonia after admission, transplant patients, those with a neoplasm who had recently received immunosuppressive treatment, leucopenia (<1000/mm^3) or neutropenia (<500/mm^3) unless attributable to pneumonia, and HIV positive patients with severe immunosuppression (CD4 <100). Patients who died within the first 48 hours after admission were not included to avoid cases that might reflect the progression of very severe illness and whose clinical course would remain unchanged despite antimicrobial therapy.

Abbreviations: CAP, community acquired pneumonia; PSI, pneumonia severity index

Definitions

Treatment failure was classified as early (<72 hours) or late (>72 hours). Late treatment failure was defined as persistence/reappearance of fever and symptoms or haemodynamic instability, the development or impairment of respiratory failure (Pao_2 <8 kPa or saturation <90% with FIO_2 of 0.21), radiographic progression, or the appearance of new infectious foci after 72 hours of antimicrobial treatment. Early treatment failure was defined as clinical deterioration within 72 hours of treatment resulting from one or more of the following causes: haemodynamic instability, appearance or impairment of respiratory failure, need for mechanical ventilation, radiographic progression, or the appearance of new metastatic infectious foci (modified from Arancibia *et al*[7]). The causes of treatment failure were classified into three categories: infectious (primary, persistent and nosocomial), non-infectious, and undetermined (according to Arancibia *et al*[7]).

Study protocol

Initial microbial studies included sputum (when possible), two sets of blood culture, and serological examination. The initial empirical antibiotic treatment was selected by the attending physician and compliance with the latest consensus Spanish guidelines SEQ-SEPAR[8] was evaluated. Treatment failure was assessed using microbiological and radiographic studies at the discretion of the attending physician. The end points of the study were the appearance of treatment failure and in-hospital mortality due to CAP and/or its complications.

Data collection

The following data were collected: age, sex, smoking and alcohol habits (>80 g/day), drug use, co-morbid disease (COPD, cardiac, liver, renal diseases, central nervous system or digestive disorders and neoplasm), influenza and antipneumococcal vaccination, antimicrobial treatment before admission, nursing home residency, and employment status. The clinical symptoms recorded included cough, expectoration, pleuritic chest pain, dyspnoea, acute confusion, signs such as temperature, rales, respiratory and heart rates, and systolic and diastolic blood pressure. The initial PSI[5] was also recorded. The number of involved lobes and the presence of cavitation or pleural effusions on the radiograph were noted and the following parameters were also recorded: leucocyte count, sodium, potassium, serum creatinine, GOT/GTP, and arterial blood gas analysis (Pao_2, $Paco_2$, Pao_2/FIO_2). The following initial empirical treatment was considered compliant with the Spanish guidelines SEQ-SEPAR[8]: (1) in hospitalised patients, third generation cefalosporin (cefotaxim or ceftriaxon) or amoxicillin-clavulanic acid with or without a macrolide, or monotherapy with fluoroquinolone; (2) in patients admitted to the intensive care unit (ICU), third or fourth generation cefalosporin associated with an intravenous macrolide (clarithromycin) or fluoroquinolone. Other antibiotic regimens were considered not to comply with guidelines.

Complications were classified as cardiac, respiratory (respiratory failure, decompensation of concomitant respiratory disease, pleural effusion), renal, digestive, and shock. The need for ICU admission and deaths were also evaluated.

Surviving patients underwent follow up radiological and serological studies after 30 days.

Quality control

The database was designed with automatic methods of data verification and detection of inconsistencies. An external monitoring agency was used to randomly verify the quality of data in half of the hospitals. The proportion of missing data was less than 5% for all factors, except for the variables COPD and influenza vaccination which reached nearly 10%.

Statistical analysis

Categorical variables were compared using the χ^2 test and the risk ratio with a 95% confidence interval was calculated. Continuous variables were compared using the Student's *t* test for independent variables. Multivariate analysis to predict treatment failure (the dependent variable) was performed using stepwise logistic regression analysis. Factors found to be significant in univariate analysis were included as independent variables. Another stepwise logistic regression analysis was performed to predict mortality (the dependent variable) using the Fine risk class, treatment failure, and initial antimicrobial treatment as the independent variables. The Hosmer and Lemeshow goodness-of-fit test was performed to evaluate the adequacy of the logistic regression models.[9] The area under the receiver-operator characteristic (ROC) curves for each mathematical model was also calculated.

RESULTS

The study group comprised 1424 patients of mean age 68 years (range 16–98). Their main demographic characteristics, co-morbidity, and risk classes are shown in table 1. The mortality rate was 5.6% and the median length of hospital stay was 9 days.

Incidence and cause of treatment failure

Treatment failure occurred in 215 patients (15.1%): 134 (62.3%) with early failure and 81 (37.7%) with late failure. The cause was infectious in 86 patients (40%), non-infectious in 34 (15.8%), and undetermined in the remaining 95 cases (44.2%), with no differences between early and late failure ($p = 0.51$). The micro-organisms most frequently isolated in treatment failure were *Streptococcus pneumoniae* (n = 21, 13 early); *Streptococcus* spp (n = 4); *Staphylococcus aureus* (n = 7, two early); *Legionella pneumophila* (n = 4); *Mycobacterium tuberculosis* (n = 4); *C burnetti* (n = 2); *Pseudomonas aeruginosa* (n = 2, both early); and Enterobacteria (n = 5, two early). A second micro-organism was also implicated in 10 patients

Table 1 Characteristics of study patients and initial risk class

No of patients	1424
Sex (M/F)	952/472
Nursing home resident	62 (4.3%)
Smoker	351 (24.6%)
Alcohol intake	189 (13.2%)
Drug user	26 (1.7%)
Previous antibiotic treatment	436 (30.6%)
Co-morbidity	1090 (76.5%)
COPD	325 (22.8%)
Asthma	104 (7.3%)
Solid non-pulmonary neoplasm	86 (6%)
Pulmonary neoplasm	13 (0.9%)
Haematological neoplasm	24 (1.6%)
Heart disease	440 (30.1%)
Diabetes	261 (18.2%)
Renal disease	102 (7.2%)
Neurological disease	207 (14.5%)
Digestive disorder	37 (2.6%)
Liver disease	87 (6.1%)
Fine risk class	
I	155 (10.9%)
II	273 (19.2%)
III	372 (26.1%)
IV	460 (32.3%)
V	164 (11.5%)

Data are presented as number (%).

(*Streptococcus* spp, n = 1; *Legionella* spp, n = 1; *P aeruginosa*, n = 5 (four early); and other micro-organisms, n = 3).

Resistant microorganisms were found in 15 patients (*S pneumoniae*, n = 6; methicillin-resistant *S aureus*, n = 4; *Klebsiella pneumoniae*, n = 1; *P aeruginosa*, n = 1; *Serratia marcescens*, n = 1; and *Acinetobacter*, n = 2).

The association of initial treatment with infectious or non-infectious failure was studied and no significant difference was found (data not shown). Co-morbidity was analysed with regard to infectious or non-infectious treatment failure and non-infectious failure was found to be more frequent than infectious failure in patients with liver (p = 0.03) and cardiac disease (p = 0.007).

Univariate analysis

Factors associated with treatment failure were classified (1) related to the host; (2) related to clinical findings in the emergency room; and (3) related to empirical antibiotic treatment.

Factors related to the host

Demographic and co-morbidity factors significantly associated with treatment failure are summarised in table 2. The duration of symptoms before admission was not significantly associated with treatment failure.

Factors related to clinical findings

Clinical, analytical and radiographic findings related to any failure and to early failure are shown in table E1 available on the *Thorax* website (www.thoraxjnl.com/supplemental). Treatment failure was most often found in risk class V (any 35%/early 13.6%) and its incidence in other classes was as follows: risk class I (16.4%/13.6%), risk class II (9.7%/5.8%), risk class III (11.7/7.1%), risk class IV (13.5/9.3%).

Factors related to empirical antibiotic treatment

The initial antibiotic treatment and its association with treatment failure are shown in table E2 available on the *Thorax* website (www.thoraxjnl.com/supplemental). Compliance with SEQ-SEPAR guidelines was achieved in 84% of patients. Significant differences were found among the different antibiotic regimes for both any failure and early failure.

Multivariate analysis: predictive model of treatment failure

Three logistic regression analyses were performed to predict any, early and late failure. In the first model (n = 939) the dependent variable was any failure (early or late failure *v* no failure) and the independent variables were all those found significant on univariate analysis (shown in table 2 and tables E1 and E2). The quantitative variables leucocytes and sodium were dichotomised as leucopenia (<4000 cell/mm^3) and hyponatraemia (<135 mEq/ml). PSI was categorised as ordinal risk class I–V and multilobar CAP was defined as more than one lobe involved. In the other two models the dependent variables were early and late failure with independent variables the same as in the first model. Patients with late failure were excluded to predict early failure and vice versa.

The predictive variables of any, early, and late failure selected by logistic regression analysis are shown in table 3. The χ^2 goodness-of-fit analysis demonstrated the adequacy of the model (p = 0.2). Influenza vaccination, COPD, and initial treatment with quinolones were found to be protective factors; in contrast, liver disease, higher risk class, multilobar CAP, leucopenia, pleural effusion, and cavitation were risk factors.

Time course and outcome

The appearance of complications, the need for admission to the ICU, and the length of hospital stay were higher in the any failure group (table 4). Details of these variables for early and late failure are shown in table E3 on the *Thorax* website (www.thoraxjnl.com/supplemental). A stepwise logistic regression was performed to predict in-hospital mortality (the dependent variable) using the following independent variables: initial antibiotic treatment, compliance with the SEQ-SEPAR guidelines (yes/no), treatment failure (yes/no),

Table 2 Host related variables in treatment failure: univariate statistical study

	Any failure			Early failure		
	%	RR (95% CI)	p value	%	RR (95% CI)	p value
Own home						
Yes	14.5	1.0		9.7	1.0	
No	26.7	2.1 (1.2 to 3.8)	0.01	16.9	1.9 (0.92 to 3.9)	0.08
Influenza vaccination						
Yes	7.5	0.3 (0.2 to 0.6)	0.001	3.4	0.25 (0.1 to 0.5)	0.001
No	17.3	1.0		11.9	1.0	
COPD						
Yes	10.5	0.6 (0.4 to 0.9)	0.01	6.3	0.5 (0.3 to 0.9)	0.01
No	16.5	1.0		11.1	1.0	
Liver disease						
Yes	24.7	1.9 (1.1 to 3.2)	0.01	14.6	1.6 (0.8 to 3.1)	0.17
No	14.5	1.0		9.8	1.0	
Pulmonary neoplasm						
Yes	24.1	1.8 (1.1 to 3.1)	0.002	30.0	3.9 (1.1 to 13.8)	0.03
No	14.6	1.0		9.9	1.0	
Haematological neoplasm						
Yes	30.4	2.5 (1.04 to 5.9)	0.04	23.8	2.8 (1.1 to 7.6)	0.03
No	14.9	1.0		9.8	1.0	
CNS disorder						
Yes	22.3	1.7 (1.2 to 2.5)	0.002	14.2	1.6 (1.1 to 2.5)	0.04
No	14	1.0		9.4	1.0	
Digestive disorder						
Yes	33.3	2.9 (1.4 to 5.7)	0.002	22.5	2.7 (1.2 to 6.1)	0.02
No	14.7	1.0		9.7	1.0	

RR, risk ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CNS, central nervous system.
Data available for each variable: own home 1414, influenza vaccination 1275, COPD 1323, liver diseases 1395, pulmonary neoplasm 1421, haematological disorder 1421, CNS disorder 1420, digestive disorder 1420.

Table 3 Results of multivariate analysis to predict treatment failure (n = 939)

	Any failure OR (95% CI)	Early failure OR (95% CI)	Late failure OR (95% CI)
Influenza vaccination	0.3 (0.2 to 0.6)	0.2 (0.1 to 0.4)	
COPD	0.6 (0.4 to 0.9)		
Liver disease	2 (1.1 to 3.5)		2.4 (1.1 to 5)
Pleural effusion	2.7 (1.8 to 4.2)	2.6 (1.6 to 4.3)	2.6 (1.5 to 4.6)
Multilobar CAP	2.1 (1.4 to 2.9)	2.2 (1.4 to 3.2)	1.7 (1.1 to 2.9)
Cavitation	4.1 (1.3 to 13.5)	5.2 (1.4 to 18.2)	
Fluoroquinolone treatment	0.5 (0.3 to 0.9)		
Fine risk class	1.3 (1.1 to 1.5)	1.2 (1.1 to 1.5)	1.4 (1.1 to 1.8)
Leucopenia	3.7 (1.4 to 10.2)	5.9 (2.2 to 15.3)	
Hyponatraemia		1.6 (1.1 to 2.4)	

COPD, chronic obstructive pulmonary disease; OR, odds ratio.
Area under ROC curve for any, early, and late failure: 0.72, 0.73 and 0.68, respectively.

and risk class (I–V). Two independent variables were selected: the initial risk class (OR 3.7, 95% CI 2.6 to 5.2) and treatment failure (OR 11, 95% CI 6.3 to 19.1). The mathematical model had an area under ROC curve of 0.90.

DISCUSSION

The most important findings of this study are that (1) the incidence of empirical treatment failure was 15% and the independent risk factors associated were multilobar CAP, cavitation on chest radiograph, pleural effusion, liver disease, leucopenia, and high PSI; (2) influenza vaccination, COPD, and treatment with quinolones were protective factors; (3) independent risk factors for early failure were pleural effusion, multilobar CAP, cavitation, leucopenia, hyponatraemia and high PSI while influenza vaccination had a protective effect; (4) late treatment failure was associated with liver disease, pleural effusion, multilobar CAP and high PSI; and (5) treatment failure increased the risk of death 11-fold after adjustment for PSI and was associated with more complications and a longer stay in hospital.

The incidence of treatment failure in hospitalised patients with CAP in our study was slightly higher (15%) than in previous studies[6 7] but lower than that reported in nosocomial pneumonia (30%).[10] The distinction between early and late failure was based on studies by Montravers *et al*[11] which showed that, after 72 hours of appropriate treatment, 88% of the patients had sterile cultures or insignificant bacterial growth, correlating with the clinical response. Ortqvist *et al*[6] also classified treatment failure as early and late with the same cut off point (72 hours). In fact, the latest ATS guidelines[12] categorise patients who do not respond adequately to antimicrobial treatment into those with lack of clinical response at day 3 after treatment and those with early clinical deterioration during the first 24–48 hours. Patients who experience early deterioration are not well characterised and merit special attention. Although some authors only consider treatment failure after 72 hours of antibiotic treatment,[6 7] we decided to maintain this concept taking into account the fact that antimicrobial treatment was not able to prevent this serious development.

The incidence of treatment failure, as expected, was higher in patients with concomitant disease although, surprisingly, it was significantly lower in COPD. In multivariate analysis COPD maintained its protective effect after adjusting for other variables. Although we do not have an explanation for this finding, concomitant treatment with steroids for regulation of the pro-inflammatory cytokine response of the host might play a part.[13 14] In fact, some studies have reported a beneficial effect of initial steroid treatment with a reduction in mortality.[15] In a multicentre study of CAP in patients with COPD in Spain[16] the mortality rate was also found to be low (8%) and, in fact, COPD is not included in the PSI score.[5] Further studies are needed to investigate the inflammatory response and the impact of concomitant treatment in these patients.

Severe pneumonias (as measured by the PSI score), multilobar disease, radiographic cavitation, and pleural effusion were associated with a 2–4-fold greater risk of treatment failure. These patients may show progressive symptoms because of persistent infection and uncommon or resistant micro-organisms.[7 17 18]

Leucopenia was also associated with an almost fourfold higher risk of any or early treatment failure. In a recent study Kolling *et al*[19] found that leucocytes had a beneficial effect in CAP, not only due to their antimicrobial activity but also because they are able to modulate the pro-inflammatory cytokine response.

Another interesting finding was the lower treatment failure in influenza vaccinated patients. This vaccine has a protective effect on the appearance of pneumonia, reduction in hospitalisation, and mortality.[20] The protective effect on treatment failure might be related to its reduction in global mortality since it particularly protects against early failure which is the cause of higher mortality. Although our study

Table 4 Time course and outcome in empirical treatment failure

Variable	Failure	No failure	p value	RR (95% CI)
Mean (SD) clinical stability (days)	11.1 (8.6)	4.1 (3.5)	0.001	
Complications (%)	69.6	23.6	0.001	7.4 (5.5 to 9.9)
Renal insufficiency (%)	21.5	6.7	0.001	3.8 (2.6 to 5.5)
Cardiac insufficiency (%)	18.2	7.	0.001	2.9 (1.9 to 4.3)
Liver disease (%)	4.2	1.1	0.001	3.9 (1.8 to 8.8)
Shock (%)	15.8	1.7	0.001	11 (6.9 to 17.8)
Respiratory insufficiency (%)	45.8	10.5	0.001	7.2 (5.3 to 9.7)
ICU admission (%)	26.2	3.9	0.001	8.6 (6 to 12.5)
Mean (SD) length of stay (days)	18.5 (13.9)	9.4 (5.7)	<0.001	
Death (%)	25.2	2.01	0.001	16 (11 to 24.6)

was observational, our findings are consistent (after adjustment for other risk variables) in showing that influenza vaccination reduces treatment failure by about one half. Antipneumococcal vaccination did not have the same effect, although the small number of patients vaccinated (2.3%) makes detection difficult.

Compliance with the Spanish guidelines, which are very similar to those recently published by the ATS,[12] was high (84%). Empirical antimicrobial treatment selected according to guidelines provides an adequate antibiotic spectrum for most pathogenic micro-organisms in CAP. Although some earlier studies did not find differences in mortality according to compliance,[21] later reports found a higher mortality, even after adjusting for initial severity, when the treatment used did not comply with the guidelines.[22–25] However, on multivariate analysis, only initial treatment with quinolones (levofloxacin 89.5%) was independently associated with lower treatment failure, although this effect disappeared when early or late failure was analysed. The newer fluoroquinolones may have contributed to our findings because of their potency, broad spectrum covering *S pneumoniae* and atypical micro-organisms, and favourable phamacokinetics. In Spain the resistance of *S pneumonia* to levofloxacin is currently very low, but it is growing in some countries and should therefore be closely monitored. The relevance of the choice of initial treatment in CAP was recently evaluated by Gleason *et al*[26] who reported a lower mortality rate with β-lactam drugs in combination with a macrolide or quinolones, and a higher risk for several other regimens. Since neither our study not that by Gleason *et al* were randomised, the patients treated with less common antibiotic schedules might correspond to those with more severe disease or with a greater probability of resistant micro-organisms. Interestingly, in a randomised trial Finch *et al*[27] found that patients treated with a fluoroquinolone (moxifloxacin) had lower mortality and a shorter length of stay in hospital than those treated with a β-lactam with or without a macrolide.

The PSI score was another independent risk factor for both early and late failure. The highest number of failures in risk class V seems reasonable although, surprisingly, we also found a treatment failure rate of 16.4% in risk class I. This may be because patients in risk class I were only admitted when they developed factors of severity such as a pleural effusion (15 patients), multilobar CAP (32 patients), or other factors such as hypoxaemia (30 patients) which were found to be associated with treatment failure. These risk factors, whose influence is underestimated by the PSI score in low risk classes, may indicate the need for hospitalisation[12] because they increase the likelihood of a complicated course.

Treatment failure increased mortality 11-fold after adjustment for risk class. The mortality was even higher in patients with early treatment failure (30% *v* 17%). In contrast to Gleason *et al*,[26] we did not find that initial empirical treatment was an independent predictor of mortality. This may be because of the smaller number of patients in our study, so the model only selected treatment failure because of its stronger association. Treatment failure was also associated with more complications and a longer stay in hospital[28] which contributes to an increase in expenses as the cost per day of hospitalisation represents the highest health care cost for CAP.[29–31]

This study has identified, at the time of hospital admission, patients who are especially prone to early and late treatment failure with an 11-fold higher mortality. Patients with liver disease, leucopenia, multilobar CAP, initial severity, and cavitation or pleural effusion on chest radiography have a higher risk of treatment failure. Since all these risk factors are independent, the probability of failure increases in relation to the number of factors and may be calculated for each patient individually. Initial treatment with quinolones was a protective factor. Vaccination against influenza was also associated with a lower risk of treatment failure and may represent a clear benefit for patients. Although these findings need to be confirmed by randomised studies, they provide a possible intervention measure to decrease mortality due to CAP. Our findings may be useful for designing future studies and health care strategies aimed at reducing mortality in CAP.

Tables E1, E2, and E3 are available online at the *Thorax* website (www.thoraxjnl.com/supplemental).

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LUNG ALERT

Which smokers will acquire COPD?

▲ Celedón JC, Lange C, Raby BA, *et al*. The transforming growth factor-β1 (TGFB1) gene is associated with chronic obstructive pulmonary disease (COPD). *Hum Mol Genet* 2004;**13**:1649–56

This study uses two sequential approaches to identify genetic determinants of COPD in the absence of α_1-antitrypsin deficiency. Firstly, using subjects from the Boston Early-Onset COPD Study ($FEV_1 \leqslant 40\%$ predicted, age <53 years, not α_1-antitrypsin deficient), linkage analysis was performed between short tandem repeat markers on chromosome 19 (this chromosome having previously been identified as linked to COPD) and physiologically based COPD phenotypes. There was significant evidence of linkage in smokers between chromosome 19q and the pre-bronchodilator FEV_1 (LOD = 3.30). This linkage peak was located near the TGFB1 gene.

Following on from this, five single nucleotide polymorphisms (SNPs) in or near the TGFB1 gene were used to look for associations between variants of TGFB1 and COPD phenotypes in two independent populations. There was a significant association between three of the SNPs and physiological COPD phenotypes in the Boston study ($n = 585$, $p<0.05$). There was also a significant association with COPD ($p \leqslant 0.02$) between three of the SNPs in subjects from the National Emphysema Treatment Trial ($n = 304$, all ex or current smokers, $FEV_1 <45\%$ predicted) compared with normal ex or current smoking controls from the Normative Aging Study ($n = 441$).

Chromosome 19q probably contains a gene that controls susceptibility to smoking induced COPD, and TGFB1 is a potential candidate for this role.

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Table E1 Variables related to clinical findings in the ER: univariate statistical study

	Any failure			Early failure		
	%	RR (95% CI)	p value	%	RR (95% CI)	p value
Symptoms						
Cough						
Yes	13.9	0.5 (0.4 to 0.8)	0.001	8.9	0.5 (0.3 to 0.7)	0.001
No	22.5	1.0		16.5	1.0	
Expectoration						
Yes	13.5	0.7 (0.5 to 0.9)	0.01	8.7	0.6 (0.4 to 0.9)	0.02
No	18.6	1.0		12.7	1.0	
Analysis						
Leucopenia						
Yes	50	5.8 (2.5 to 13.3)	<0.001	45	7.8 (3.3 to 18.6)	0.001
No	14.6	1.0		9.3	1.0	
Hyponatremia						
Yes	19.7	1.6 (1.2 to 2.1)	0.003	14.5	1.8 (1.3 to 2.7)	0.003
No	13.5	1.0		8.4	1.0	
Radiographic findings						
Cavitation						
Yes						
No	37.5	3.4 (1.3 to 8.9)	0.01	28.5	3.6 (1.2 to 10.9)	0.02
Pleural effusion	14.9	1.0		9.8	1.0	
Yes						
No	29	2.6 (1.8 to 3.7)	0.001	19.6	2.6 (1.6 to 3.9)	0.001
Multilobar CAP	13.3	1.0		8.7	1.0	
Yes						
No	24	2.2 (1.6 to 3.1)	0.001	17.3	2.4 (1.6 to 3.5)	0.001
	12.3	1.0		8	1.0	

ER, emergency room; RR, risk ratio; CI, confidence interval.

Data available for each variable: cough 1412, expectoration 1407, leucopenia 1416, hyponatremia 1416, cavitation 1412, pleural effusion 1419, multilobar CAP 1392.

Table E2 Results of initial antimicrobial treatment and failure

	Patients receiving (%)	Any failure* (%)	Early failure * (%)
3rd generation cephalosporin	8.8	16	12
3rd generation cephalosporin + macrolide	34.4	14.8	9.8
Amoxicillin- clavulanic acid	20.1	14	7.2
Amoxicillin-clavulanic acid + macrolide	3.8	11.3	3.7
Fluoroquinolone**	16.6	10.4	5.6
Others	16.1	20.2	13.9

*$p < 0.05$.

** Levofloxacin 89.5%, moxifloxacin 5.7%, ciprofloxacin 4.8%.

Table E3 Evolution and outcome in the group of empirical treatment failure

Variable	Early failure	Late failure	p value
Mean (SD) clinical stability (days)	10.8 (8.9)	11.5 (8.3)	0.46
Complications (%)	73	62.9	0.09
Renal insufficiency (%)	24	17.3	0.2
Cardiac insufficiency (%)	17.3	19.7	0.6
Liver disease (%)	3.7	4.9	0.6
Shock (%)	19.5	9.8	0.06
Respiratory insufficiency (%)	49.6	39.5	0.1
Empyema (%)	12	12.3	0.9
ICU admission (%)	30.8	18.5	0.04
Mean (SD) length of stay (days)	15.9 (12.1)	22.7 (15.6)	<0.001
Death (%)	30.1	17.2	0.03