Markers of treatment failure in hospitalised community acquired pneumonia

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ABSTRACT

Background: Lack of response to treatment in community acquired pneumonia (CAP) worsens outcome. We evaluated the systemic cytokine profile (tumour necrosis factor α, interleukin (IL)1, IL6, IL8 and IL10), C reactive protein (CRP) and procalcitonin (PCT) in patients with CAP who had treatment failure.

Methods: A prospective study was performed in hospitalised patients with CAP. Cytokines, PCT and CRP measurements were obtained on day 1 and after 72 h of treatment. Treatment failure was the endpoint evaluated, with separation of those with early ($\leqslant$72 h) or late failure.

Results: 453 patients were included: 84 (18%) had treatment failure, of whom 38 (8%) were early failures. Median levels of IL6, PCT and CRP on days 1 and 3 and median levels of IL8 on day 1 were significantly higher in patients with any treatment failure. Logistic regression analysis demonstrated that values above the cut-off points for IL6 ($\geqslant$169 pg/ml), IL8 ($\geqslant$14 pg/ml) and CRP ($\geqslant$21.9 mg/dl) on day 1 had independent predictive value for any treatment failure after adjustment for initial severity; relative risks (OR) found were 1.9, 2.2 and 2.6, respectively. Increased levels for CRP and PCT on day 1 were also independent predictors for early failure. Increased levels for IL6 and CRP were the best predictors of late failure.

Conclusions: Serum levels of CRP, IL6 and PCT on days 1 and 3 were independently associated with a higher risk of any treatment failure. Low levels of PCT and CRP on day 1 had a high negative predictive value for early failure.

Community acquired pneumonia (CAP) continues to be a serious health problem worldwide, with an incidence ranging from 3 to 5 cases per 1000 inhabitants among adults, and a mortality in hospitalised patients of 5–15%, serving as the number one cause of death from infectious diseases.[1 2] Most patients hospitalised for CAP respond satisfactorily to treatment but approximately 10–15% develop treatment failure and almost 6% may manifest rapidly progressive and life threatening pneumonia.[3–5] It has been shown that death from CAP occurs primarily in patients with therapeutic failure, reaching rates of up to 40% in this population.[3–5]

Factors associated with a lack of response to empiric antibiotic treatment are not completely known. Adequate response to infection is complex and requires appropriate and timely therapy along with the development of an appropriate initial inflammatory response to contain the proliferation and dissemination of the microorganisms, followed by a compensatory phase to restore initial homeostasis.[6] It has recently been recognised that an excessive systemic proinflammatory response in patients with sepsis and severe CAP is associated with deleterious effects and a worse prognosis.[7 8] The presence of an excess of proinflammatory cytokines has mainly been associated with initially severe illness, as well as with altered genetic susceptibility of individual patients.[9] It has also been suggested that an exaggerated anti-inflammatory response, with an increase in interleukin (IL)10, may have a negative effect on the resolution of infection. Nonetheless, the balance of proinflammatory/anti-inflammatory cytokines in patients with treatment failure has not been investigated thoroughly. Previous studies have been performed on some biological markers of infection,[10 11] such as C reactive protein (CRP) and procalcitonin (PCT), as markers of treatment failure, with promising initial results.[12–14]

We hypothesised that patients who develop treatment failure have higher initial and persistent higher levels of systemic cytokines and biological markers than those without treatment failure. If true, then biological markers could be useful to supplement prognostic scoring systems in order to identify patients with a greater probability of deteriorating who would require a high level of monitoring.

The aim of the present study was to investigate the systemic inflammatory response of tumour necrosis factor α (TNFα), IL1, IL6, IL8 and IL10, and serum biological markers of infection, such as CRP and PCT, in patients admitted for CAP, and to determine their relationship with treatment failure, both early and late. Measurements of systemic levels of cytokines and serum markers were performed on day 1 and after 72 h of antibiotic treatment.

PATIENTS AND METHODS

A prospective study was performed in patients with CAP consecutively admitted to two hospitals from October 2003 to June 2004. Inclusion criteria were the presence of a new radiographic infiltrate and at least two compatible clinical symptoms. Exclusion criteria were admission in the previous 15 days, immunosuppressive treatment and/or corticosteroids (>15 mg/day of prednisone or its equivalent), leucopenia <1000/mm or neutropenia <500/mm (except if attributable to CAP) and HIV positive with a CD4 count <100. The study was approved by the ethics committee and patients provided informed consent.

The following data were recorded: age, gender, smoking history, alcohol abuse (>80 g/day) and

Table 1 Characteristics, comorbidity and initial severity in the group with treatment failure and in the control group

Characteristic	Failure yes (n = 84)	Failure no (n = 369)	p Value
Age (y) (mean (SD))	68 (17)	67 (17)	0.48
Sex (F/M)	33/51 (39/61)	138/231(37/63)	0.78
Long term care facility	6 (7)	18 (5)	0.40
Smoking	21 (25)	78 (21)	0.44
Alcohol	9 (11)	42 (11)	0.86
Cardiac failure	15 (18)	61 (16)	0.76
Renal failure	2 (2)	23 (6)	0.16
Diabetes	14 (17)	77 (21)	0.38
Liver disease	3 (4)	9 (2)	0.16
COPD	13 (16)	66 (18)	0.60
Neurological disease	23 (27)	75 (20)	0.17
Neoplasm	4 (5)	15 (4)	0.75
ICU admission	22/84 (26)	11/369 (2.9)	0.001
Risk class of Fine			0.04
I	7 (8)	41 (11)	
II	9 (11)	64 (17)	
III	11 (13)	84 (23)	
IV	30 (36)	137 (37)	
V	27 (32)	43 (12)	

Data are number (%) of patients, unless otherwise indicated.
COPD, chronic obstructive pulmonary disease.

comorbidities (chronic obstructive pulmonary disease (COPD), cardiac, liver, renal or central nervous system diseases). The initial risk class, according to the pneumonia severity index measured by Fine risk classes,[15] was also recorded.

Empiric antimicrobial treatment was considered adequate when it was active against the causal microorganism if identified.

Definitions
The definition of treatment failure was slightly modified from that of a prior publication.[4] Early treatment failure was defined as clinical deterioration within 72 h of treatment, as indicated by the need for mechanical ventilation and/or shock,[16] or death. Late treatment failure was defined as persistence or reappearance of fever (>37.8°C),[17] [18] radiographic progression (>50% increase),[19] including pleural effusion and/or empyema, nosocomial infection,[3] impairment of respiratory failure (defined as PO_2/FiO_2 <250 with respiratory rate ≥30/min) and need for mechanical ventilation or shock after 72 h.[18]

Cytokines, PCT and CRP determinations
Blood samples were obtained on the first day and after 72 h of treatment, centrifuged, coded and frozen at –80°C until analysis. Determination of IL6, IL8, IL10 and TNFα levels was performed using a commercial enzyme immunoassay technique (Biosource, Nivelles, Belgium). Limits of detection were: IL6 2 pg/ml; TNFα 3 pg/ml; IL8 0.7 pg/ml; and IL10 1 pg/ml.

An immunoluminometric technique was used to measure PCT (Liaison Brahms PCT; DiaSorin, Saluggia, Italy) with a detection limit of 0.3 ng/ml. CRP was measured with an immunoturbidimetric method using a commercially available test (Bayer Diagnostics, Leverkusen, Germany) with an Advia 2400.

Statistical analysis
Statistical analysis was performed using the SPSS 12.0 software program. The χ^2 test was used for qualitative variables and the Student's t or the Mann-Whitney U test was used for quantitative variables. Diagnostic value was assessed calculating the area under the receiver operating characteristic curves.

Multivariate logistic regression analyses were performed to predict any, early and late treatment failure (dependent variables). For early failure prediction, patients with late failure were excluded, and vice versa. For the prediction of any failure (dependent variables), two logistic regression analyses were performed for each dependent variable: the first from measurements of cytokines, CRP and PCT obtained on day 1; and the second from measurements both on days 1 and 3 as independent variables. Independent variables were initial severity, comorbid condition, cytokine levels and markers. CRP and PCT levels, as well as cytokine levels, were dichotomised using the values of the 75th percentile for each marker in the non-treatment failure group as the cut-off as follows: CRP day 1 ≥21.9 and day 3 ≥9.6; PCT day 1 ≥2.2 and day 3 ≥0.7; TNF day 1 ≥45 and day 3 ≥45; IL1 day 1 ≥36 and day 3 ≥28; IL6 day 1 ≥169.3 pg/ml and day 3 ≥73.2 pg/ml; IL8 day 1 ≥14 pg/ml and day 3 ≥14 pg/ml; IL10 day 1 ≥19 pg/ml and day 3 ≥15 pg/ml. Comorbid conditions were included in the model and dichotomised into "yes" or "no". These conditions were: COPD, cardiac, liver, renal and CNS diseases. Initial severity was categorised as high (Fine risk classes IV–V) or low (classes I–III).[15]

RESULTS

Patient population
During the study period, 453 patients were prospectively followed (mean age 67.3 (SD 17.1) years): 84 (18%) developed treatment failure of whom 38 (8%) had early failure. The main demographic characteristics, comorbidity and risk class of Fine for each group are shown in table 1. No significant differences were found between the two groups except for initial severity and ICU admission.

Patients with treatment failure had the same distribution of risk class of Fine as those without, although the number of patients with risk classes IV and V was higher in patients with treatment failure than in those without. Severity of illness at ICU admission showed higher percentages of patients with treatment failure. Shock at admission was present in 10 patients with treatment failure compared with none in those without (p<0.001). Thirty-one patients died (6.8%): nine of 38 with early failure (24%) and 20 of 46 with late failure (43.7%).

The causal microorganism was found in 198 patients (44%): 81 *Streptococcus pneumoniae* (18%), 17 *Legionella pneumophila* (4%), 12 *Staphylococcus aureus* (3%), 12 *Haemophilus influenzae*, 11 *Pseudomonas aeruginosa*, five *Mycoplasma pneumoniae*, six *Escherichia coli* and 28 other microorganisms. We found a mixed aetiology in 26 patients: 15 had *S pneumoniae* together with another microorganism.

For the group with treatment failure, recovered microorganisms and causes of treatment failure are summarised in table 2.

In 36 patients (8%) with treatment failure, a microbiological diagnostic was not reached, and a non-infectious aetiology was present in two patients.

Causes of early failure were: shock (n = 12), need for mechanical ventilation (n = 12), shock and mechanical ventilation (n = 6), and nine of 38 died within the first 72 h. Causes of late failure were: mechanical ventilation and/or shock (n = 17), persistence of fever and radiological progression with or without pleural effusion (n = 13), persistence of fever and symptoms >72 h (n = 12) and hospital acquired infection (n = 4).

Table 2 Treatment failure group. Causal microorganism and initial empirical treatment

Microorganism	Treatment Antibiotic (cases)	Pathogen sensitivity to antibiotic	Cause of treatment failure
S pneumoniae	Cef+MCL (8)	8 Sensitive	Shock (6) (1MV)
			Persistence of fever (2): 1 with pleural effusion
S pneumoniae	Cef+Levofl (5)	5 Sensitive	Shock and/or MV (2)
			Radiographic progression (2)
			Empyema (1)
S pyogenes	Cef+ MCL(1)	1 Sensitive	Shock (1)
Legionella	Beta lactam+MCL (2)	5 Sensitive	Impairment respiratory failure (2)
	Beta lactam+ Levofl (3)	5 Sensitive	Shock (3) (2MV)
S aureus	Cef+MCL (2)	4 Sensitive	MV and/or shock (3)
	Levofl (1)		Nosocomial infection (1)
	Piper+cefepime (1)		
MR S aureus	Cef+MCL (1)	1 Resistant	MV and/or shock (1)
Pseudomonas	Cef+MCL/Levofl (2)	2 Resistant	MV and shock (2)
	Cefepime+MCL (1)	1 Sensitive	Nosocomial infection (1)
	Levofl (1)	1 Resistant	Persistence of fever (1)
Pseudomonas+MRSA	Cefepime+ciprofl (1)	MRSA resistant	MV and shock (1)
H influenza	Cef+Levofl (2)	3 Sensitive	MV (2)
	Cef+MCL (1)		Persistence of fever and pleural effusion (1)
E coli	Beta lactam+MCL (4)	1 Resistant	Impairment of respiratory failure (2)
		3 Sensitive	Shock (2) (1MV)
			Impairment of respiratory failure (2), shock (2) (1MV)
E coli+ S aureus	Cef+MCL (1)	1 Sensitive	MV and shock (1)
Enterococcus	Levofl (1)	2 Resistant	Persistence of fever (2)
	Beta lactam+MCL (1)		
Anaerobios	Cef+MCL (1)	1 Resistant	Persistence of fever and pleural effusion (1)
Nocardia	Cef+Levofl	1 Resistant	Shock (1)
Fungi	Cef+MCL (1)	1 Resistant	Persistence of fever (1)
Tuberculosis	Cef+MCL (1)	2 Resistant	Persistence of fever (2)
	Levofl (1)		
Acinetobacter	Cef+MCL	1 Resistant	MV and shock (1)
Morganella	Imipenem	1 Sensitive	MV and shock (1)

Beta lactam, Coamoxiclav or cephalosporin 3rd or 4th generation; Cef, 3rd generation cephalosporin; Ciprofl, ciprofloxacin; Levofl, levofloxacin; MCL, macrolide (clarithromycin or azithromycin); MRSA, methicillin resistant *Staphylococcus aureus*; MV, mechanical ventilation; Piper, piperacillin-tazobactam.

Table 3 Results of cytokines and markers on days 1 and 3 in the groups with treatment failure (early and late) and without treatment failure

Cytokines	Total treatment failure No (median (P$_{25}$–P$_{75}$))	Yes (median (P$_{25}$–P$_{75}$))	p Value	Early versus late failure Early failure (median (P$_{25}$–P$_{75}$))	Late failure (median (P$_{25}$–P$_{75}$))	p Value
Day 1						
CRP (mg/dl)	13.6 (6.8–21.9)	23.2 (15.9–31)	0.0001	22.9 (11.6–35.0)	25.6 (16.9–30.4)	0.94
PCT (ng/ml)	0.5 (0.3–2.2)	1.5 (0.4–7.1)	0.0001	3.36 (0.86–23.25)	1.07 (0.42–4.04)	0.01
TNFα (pg/ml)	29 (17–45)	33 (19–56)	0.11	40 (22–88)	29 (17–55)	0.15
IL1 (pg/ml)	21 (8–36)	16 (0–48)	0.37	6 (0–30)	18 (6–61)	0.08
IL6 (pg/ml)	66 (25–169)	187 (71–779)	0.0001	145 (38–1288)	191 (99–414)	0.69
IL10 (pg/ml)	7 (2–19)	9 (0–36)	0.35	15 (1–59)	5 (0–29)	0.11
IL8 (pg/ml)	5 (1–14)	13 (5–56)	0.0001	13 (5–63)	14 (4–43)	0.70
Day 3						
CRP (mg/dl)	4.5 (1.9–9.6)	12.1 (4.6–19.8)	0.0001	5.2 (2.7–11.9)	16.5 (8.4–21.9)	0.0001
PCT (ng/ml)	0.3 (0.2–0.7)	0.5 (0.3–1.5)	0.004	0.48 (0,25–2.15)	0.53 (0.32–1.00)	0.58
TNFα (pg/ml)	27 (14–45)	28 (14–41)	0.64	25 (13–41)	29 (14–42)	0.91
IL1 (pg/ml)	14 (4–28)	17 (0–40)	0.74	0 (0–22)	23 (8–62)	0.0001
IL6 (pg/ml)	30 (9–73)	102 (27–191)	0.0001	36 (8–132)	129 (39–229)	0.004
IL10 (pg/ml)	5 (1–15)	6 (0–19)	0.74	7 (0–11)	3 (0–28)	0.73
IL8 (pg/ml)	7 (2–14)	9 (3–21)	0.37	6 (2–14)	10 (2–32)	0.20

CRP, C reactive protein; IL, interleukin; P25–P75, percentile 25–percentile 75; PCT, procalcitonin; TNFα, tumour necrosis factor α.

Table 4 Sensitivity, specificity and predictive values of markers on day 1 to predict early failure

	Early failure			
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CRP	54	72	16	94
CRP+Fine risk classes IV–V	45	87	23	94
PCT	57	75	17	95
PCT+Fine risk classes IV–V	45	85	22	94
CRP+PCT	45	89	28	95
CPR+PCT+Fine	37	94	38	94

CRP, C reactive protein; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value.

Initial antimicrobial treatments prescribed in the whole group were: 261 (58%) beta lactam (ceftriaxone/cefotaxime/cefepime or co-amoxi-clavulanate) with a macrolide (clarithromycin or azithromycin), 43 of whom developed treatment failure (16%); 104 (23%) fluorquinolone (levofloxacin), with nine developing treatment failure (9%); 31 (7%) beta lactam with quinolone, 19 of whom had failure (61%); 28 (6%) beta lactam as monotherapy, four developing failure (14%); and 29 (6%) other regimens, nine of whom had failure (31%). Table 2 summarises the initial antibiotic treatment and aetiology in the treatment failure group. Inadequate initial treatment was present in 14 of 46 patients (17%) with a known causal microorganism in the treatment failure group versus 19 out of 152 patients (5.6%) in the non-failure group (p:0.007).

Initial severity, systemic cytokines, markers and treatment failure

Serum levels of cytokines, CRP and PCT on days 1 and 3 in relation to any treatment failure, as well as early and late failure, are summarised in table 3.

Overall, concentrations of these markers decreased from day 1 to day 3. Significantly higher levels of CRP, PCT, IL8 and IL6 on day 1 were present in patients with any treatment failure compared with those with no failure. Levels of CRP, PCT, IL1 and IL6 on day 3 were also higher in those with failure compared with those without. When comparing those with early and late failure, there were higher initial levels of PCT on day 1 in patients with early failure. On day 1, median PCT levels were significantly higher in more severely ill patients (Fine risk classes IV–III) compared with lower risk class patients (I–III) (1.1 vs 0.4 ng/ml; p<0.001). However, no significant differences were found for IL6, IL8 or CRP on day 1 when comparing those

with early and late failure. On day 3, those with late failure compared with those with early failure had higher levels of CRP, IL1 and IL6. On day 3, a significant elevation in PCT was found in risk classes IV–V compared with the lower risk class (0.5 vs 0.3; p<0.002). No differences were found in levels of CRP, PCT or cytokines on days 1 and 3 when comparing patients with treatment failure due to an infectious aetiology with those of an unknown aetiology.

The diagnostic value of CRP and PCT for predicting early failure was calculated using as the threshold value the 75th percentile in the non-treatment failure group. The results are shown in table 4.

Both markers showed moderate sensitivity with low positive predictive values and high negative predictive values. When adding the initial severity measured by risk class of Fine, the diagnostic value of these markers did not improve. The highest diagnostic value was reached when both markers were used together.

Multivariate analysis: predictive model of therapeutic failure

The results of the three multivariate analyses to predict any, early or late treatment failure are shown in table 5.

When determinations on day 1 only were used, the model found that IL6, IL8 and CRP values predicted any treatment failure. When data from both days 1 and 3 were included, to predict any failure, the model identified measurement on day 3 of IL 6 (OR 2.6) and CRP (OR 3.4) as the strongest predictors of treatment failure. For early failure, only measurements obtained on day 1 were included as independent variables, whereas for predicting late failure, only values on day 3 were included as independent variables. When using determinations performed on day 1 for predicting early failure, CRP and PCT were the strongest predictors of early failure, while using determinations performed on day 3 to predict late failure, IL6 and CRP levels were the strongest predictors. The χ² goodness of fit analysis demonstrated the adequacy of the models (p>0.05).

DISCUSSION

The most important findings of this study are: (1) median levels on both day 1 and day 3 for IL6 and the biological markers PCT and CRP were significantly higher in patients with any treatment failure compared with those without treatment failure; (2) on day 1, an increase in both CRP (OR 2.6) and PCT (OR 2.7) above a dichotomous threshold (75th percentile of the value in non-treatment failure) resulted in good prediction of early failure; (3) when CRP or PCT did not exceed the threshold

Table 5 Results of three logistic regression analyses to predict treatment failure, early and late

	Treatment failure		Early failure		Late failure	
Measurements	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Day 1						
IL6 (pg/ml)	1.9 (1.1–3.4)	0.02	—	—	2.3 (1.1–4.7)	0.02
IL8 (pg/ml)	2.2 (1.3–3.9)	0.003	—	—	2.8 (1.4–5.7)	0.003
CRP (mg/dl)	2.6 (1.5–4.6)	0.001	2.6 (1.2–5.5)	0.01	2.6 (1.3–5.3)	0.009
PCT (ng/ml)	—	—	2.7 (1.3–5.8)	0.01	—	—
Fine IV-V vs I-III	1.7 (1.1–2.9)	0.04	2.6 (1.2–5.9)	0.01	—	—
Day 1 and 3						
IL6 day 3 (pg/ml)	2.6 (1.3–5,3)	0.005	—	—	4.2 (1.8–9.6)	0.001
CRP day 3 (mg/dl)	3.4 (1.7–6.7)	0.001	—	—	4.8 (2.1–11.2)	0.0001
Fine IV-V vs I-III	1.9 (1.1–3.6)	0.04	—	—	—	—
PCT day 3 (ng/ml)	—	—	—	—	—	—

CRP, C reactive protein; IL, interleukin; PCT, procalcitonin.

values on day 1, there was a strong negative predictive value for early failure; and (4) elevated levels of IL6 and CRP above threshold values on day 3 were the best predictors of late treatment failure.

In previous studies, treatment failure was observed in only 2% of ambulatory patients[20] but in 15% of those hospitalised for CAP, playing an important role in determining the final prognosis of this infection as mortality was high in these patients who failed.[4] Early failure and/or progressive pneumonia are often related to physiological deterioration with a high mortality rate.[4 18] Identification of this population represents a challenge for clinicians because prognostic scales are insufficient and it represents a clear opportunity for implementing strategies to improve the prognosis of CAP. In our study, early failure was more common in patients with Fine risk classes IV and V, compared with those in classes I, II and III, and also in patients admitted to the ICU, and in those with shock at admission, compared with that observed in patients without failure. In addition, in our multivariate model, serum cytokines and markers were good predictors of early failure, and adding the Fine risk classes did not improve the values for sensitivity or negative predictive value. Given their worse prognosis, those at risk for early failure could be considered a target for studies with early intervention of non-antibiotic therapies such as drotrecogin alfa (activated) or corticosteroids.

In this study, we confirmed that there was a systemic increase in proinflammatory cytokines and the biological markers CRP and PCT on the first day, with a reduction after 72 h of treatment. Interestingly, on day 1, PCT levels were higher in those with early versus late failure whereas CRP, IL8 and IL6 showed similar levels in those with early and late failure. Thus increases in PCT on day 1 might be useful to discriminate between those with early and late failure. This finding may be clinically important for the differences in prognosis between these groups. In fact, patients with early failure have the greatest probability of dying, thereby requiring more rapid intervention and close monitoring.

After 72 h of antibiotic treatment, a systemic reduction in cytokines and biological markers was observed in the entire group of patients. However, significantly higher values for IL6, IL1, PCT and CRP on day 3 were found in patients with therapeutic failure compared with those without, and all of these values, except PCT, were associated with late failure, compared with early failure. The reduction in CRP values in the first 4 days of CAP has been related to adequate therapeutic response.[14 21] Luyt et al[13] also found that values of PCT were predictive of failure in ventilator associated pneumonia, with a poor outcome being associated with higher levels on the third and seventh days of treatment.

The distribution of antimicrobial regimens was similar between the patients with treatment failure and the remainder of the cohort, although those treated with fluoroquinolones had a lower percentage of treatment failure while those treated with a beta lactam with a quinolone had a higher rate of treatment failure. When initial antimicrobial therapy was evaluated in relation to microbiological results, we found that inadequate therapy was present in 17% of those with treatment failure compared with only 5% in those without. In those with treatment failure and a known aetiology, inadequate treatment was detected if there was an unusual microorganism, but rarely because of antimicrobial resistance. An interesting finding is that even patients with adequate antimicrobial treatment (83% of those with treatment failure), most with *S pneumoniae* CAP could develop treatment failure, highlighting the importance of the host response.

As treatment failure may be related to different factors,[4] we performed a multivariate analysis to evaluate the independent effect of inflammation, as reflected by levels of cytokines and systemic markers. In fact, some previous studies have found higher cytokine levels in more severely ill patients.[22–24] Masía and colleagues[25] have also found that serum PCT values correlated with initial severity, as measured by Fine risk class, and Prat and colleagues[26] made similar observations in patients with bacteraemic pneumonia. Thus after adjusting for initial severity and comorbidity, we demonstrated an independent predictive value for any treatment failure of increases in day 1 levels of CRP, IL8 and IL6. When measurements from day 3 were introduced into the model, the strongest predictors of any treatment failure were determinations performed on day 3 instead of day 1, and were levels of IL6 and CRP that were above the dichotomous threshold value. This finding is consistent with other studies which have found that a reduction in levels of inflammatory mediators at day 3 were associated with a good response.[12 14 27] Interestingly, we found that early failure was increased almost fourfold in patients with levels of CRP and PCT that exceeded the threshold value on the first day, regardless of the Fine risk class. In addition, day 1 levels of CRP and PCT below this threshold have a high negative predictive value for early failure. This finding may help clinicians to identify, early on, patients at risk for early failure who might benefit from an initial aggressive antibiotic and non-antibiotic management (ie, ICU admission, steroids).[28 29]

Studies on the profile of response of proinflammatory cytokines in the lung itself are not practical in clinical practice and thus study of the kinetics of serum levels of biological markers of infection are becoming relevant to evaluate therapeutic response,[30] and eventually to design treatment strategies aimed at modulating response.[8 31 32] We found an independent predictive value for biological markers to predict early failure. In summary, we observed that patients with treatment failure showed an increase in systemic proinflammatory response on the first day and after 72 h of treatment compared with those with a good response. Serum levels of CRP, PCT and IL6 measured on days 1 and 3 might be useful as predictors of treatment failure in CAP. Early failure is less likely in those patients with low levels of PCT and CRP on day 1 because of the high negative predictive values found for these markers. Late treatment failure is best predicted by high levels on day 3 of IL6 and CRP. Further studies are needed to confirm our results in order to establish whether this information added to prognostic risk scales allows the identification of a target population with a higher risk of deterioration and poor prognosis.

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Lung alert

Snoring is more strongly associated with chronic bronchitis in non-smokers

It has been suggested that patients with chronic bronchitis are more likely to snore during sleep. The authors studied 5015 people in Korea aged 40–69 years who all participated in a comprehensive health examination and on-site interview. Participants who reported symptoms suggesting chronic bronchitis or a previous diagnosis of chronic obstructive pulmonary disease who did not complete questions related to snoring, whose smoking status was not reported or who reported pregnancy during follow-up were excluded.

A total of 4270 participants (52% men) entered the analysis for the first 2 years. Participants were asked about the presence and frequency of snoring. Baseline demographic data showed that frequent snorers were more likely to be older, male, working, heavier, alcohol-consuming smokers and with a history of exposure to chemicals.

During a 4-year follow-up period, 314 new cases (27.1 cases per 1000 person-years) of chronic bronchitis were identified. Follow-up of these patients showed that snoring frequency had a positive linear relationship with the risk of chronic bronchitis. Stratified analysis by smoking showed an association between snoring and chronic bronchitis in never smokers, while a non-significant association was seen in former and current smokers. A similar significant association between snoring and chronic bronchitis was observed among house workers, which was probably related to the association seen in non-smokers since most house workers studied were non-smoking women.

This study provides support for the hypothesis that snoring is associated with chronic bronchitis. As the study did not explore the mechanism of how snorers may develop chronic bronchitis, further investigation is needed to determine the link between these conditions.

▶ Baik I, Kim J, Abbott RD, et al. Association of snoring with chronic bronchitis. *Arch Intern Med* 2008;**168**:167–73.

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