IgG subclasses in previously healthy adult patients with acute community-acquired pneumonia

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Objective. To measure IgG antibody subclasses in previously healthy adult patients with acute community-acquired pneumonia, and to assess any association between differences of subtype levels and severity of illness or prognosis.

Design. Prospective study.

Setting. The intensive care unit (ICU) and general medical wards of Hillbrow Hospital, Johannesburg, an urban general hospital.

Patients. Sixty-six previously healthy adult patients with acute community-acquired pneumonia, of whom 47 were considered less severely ill, while 19 were admitted to an ICU.

Outcome measures. Measurement of IgG subclass levels and determination of any association between differences in subtype levels and various poor prognostic factors in pneumonia, need for ICU admission, complications of illness, and APACHE II score of ICU cases or outcome of patients.

Results. A number of statistically significant differences ($P < 0.05$) were noted between the two groups of patients (critically ill v. others) representing well-known negative prognostic factors in pneumonia. A greater degree of tachycardia and tachypnoea and extremes of white cell count, a higher serum urea concentration and multilobar pulmonary consolidation characterised the patients in the ICU. In addition, the mortality rate in the ICU patients was significantly greater ($P < 0.0001$). Similar findings were noted when survivors and non-survivors were compared. Few abnormalities of IgG subclass levels were noted in the various patient groups, which did not allow adequate analysis of their clinical significance.

Conclusion. This study demonstrated a small number of abnormalities in IgG subclass levels in previously healthy adult patients with acute community-acquired pneumonia.

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Community-acquired pneumonia continues to be associated with morbidity and mortality in patients worldwide. With regard to risk factors for the development of pneumonia, it has been known for more than 20 years that certain patients with IgG subclass deficiencies may develop recurrent respiratory tract infections, including pneumonia.[1-4] However, there are few studies of IgG subclass levels in previously healthy adult patients with acute community-acquired pneumonia,[5-6] particularly of patients admitted to an intensive care unit.

The primary aim of the current investigation was to record the IgG subclass levels in critically ill patients admitted to an intensive care unit (ICU) and patients with less severe cases of acute community-acquired pneumonia, and to determine any association between alterations in these values and patient prognosis.

Patients and methods

This project was a prospective study of previously well adult patients with acute community-acquired pneumonia, conducted at Hillbrow Hospital, Johannesburg. Permission to conduct the study was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand. This study was continued with the intention of recruiting 50 non-severely ill and 20 critically ill patients with pneumonia.

For the purposes of the study, community-acquired pneumonia was defined as an acute, pyrexial lower respiratory tract infection, acquired in the community and associated with clinical and radiological evidence of consolidation of the lung(s). The data recorded for each patient, if available, were demographic details including age and gender, clinical features including initial blood pressure, pulse and respiratory rates, and laboratory data including results of haematological, biochemical and microbiological testing, as well as features of the chest radiograph. The collection of these data allowed calculation of the APACHE II score for the ICU patients only. For the purposes of the microbiological data, results of the Gram stain and culture of good-quality sputum specimens as well as of blood cultures taken before initiation of antibiotic therapy were recorded. In 1 patient the microbiological data were based on serological testing for *Mycoplasma pneumoniae*.

Testing for IgG subclass levels was undertaken by means of laser nephelometry with appropriate test kits (Binding Site Ltd, Birmingham, England) and levels were assessed in a Behring Nephelometer 100 Analyser (Behring Diagnostika, Germany).

Statistical analysis was by means of Student's *t*-test, the Mann-Whitney (2-tail) U-test for difference of two medians of continuous variables, and Fisher's exact (2-tail) test for 2 x 2 contingency tables of categorical variables. For the comparison of the IgG subclass values in the various groups, the data on subclass levels were used both as categorical variables (normal, high or low) and continuous variables (mean values).

Results

A total of 66 patients with pneumonia were recruited, 19 in the ICU and 47 who were less severely ill.

ICU cases

Of the ICU patients, 17 were men and 2 women, with an age range of 18 - 62 years. The mean APACHE II score for the ICU cases was 17.6. A microbiological diagnosis was made in 12 of these patients (63%). The commonest isolate was *Streptococcus pneumoniae* (8 cases, 6 isolates from blood culture). Additional organisms isolated from blood culture were *Klebsiella pneumoniae* (2 cases), and *S. pyogenes* (1 case). A diagnosis of *M. pneumoniae* pneumonia was made in 1 case on the basis of serological testing. Ten patients had multilobar (53%) and 9 unilobar (47%) pulmonary consolidation.

As expected, several clinical and laboratory features differentiated the ICU group from the less severely ill patients (Table I). In particular, more severe tachycardia and tachypnoea, extremes of white cell count derangement, higher serum urea values and multilobar pulmonary consolidation characterised those patients in the ICU. There was no difference in systolic or diastolic blood pressure between the two groups. Table II shows the abnormalities of IgG subclass levels documented. Abnormalities of IgG subclass levels (positive or negative differences) were seen in 10 patients, with no association between these differences (either overall differences or deficiencies alone) and any of the other negative prognostic factors, the APACHE II score or outcome. There was no significant difference in the number of patients with subclass differences, or in the mean values of any of the subclasses when ICU patients were compared with non-ICU patients. A total of 14 of the ICU patients required mechanical ventilation, and 16 required inotropic support of the blood pressure. Complications that occurred in patients who survived included pleural effusion in 4 cases, nosocomial pneumonia in 2, and acute respiratory distress syndrome and meningitis in 1 patient each. Ten of the patients died (a 53% mortality rate), compared with 1 of the less severely ill patients (a 2% mortality rate). This difference was statistically significant ($P < 0.00001$). While there was a tendency towards a higher APACHE II score in the non-survivors (mean 19.7 v. 15.3), this difference did not reach statistical significance, probably owing to low patient numbers.

Non-ICU cases

Among less severely ill patients were 31 men and 16 women with an age range of 15 - 71 years. An organism was isolated in 12 cases (26%). The commonest isolate was *S. pneumoniae* (6 cases; 3 isolates from blood culture). Additional organisms isolated from blood culture were *S. viridans* (2 cases) and, from sputum culture, *Haemophilus influenzae* or *H. parainfluenzae* (4 cases), and 1 each of *K. pneumoniae* and *Moraxella catarrhalis*. Multilobar pulmonary consolidation was found in 10 cases (21%) and unilobar consolidation in 37 (79%). As expected, a number of features differentiated these patients from the critically ill patients, as shown in Table I.

Table I. Differences found in clinical and laboratory features of critically ill and less severely ill patients with acute community-acquired pneumonia

	Critically ill ($N = 19$)	Not severe ($N = 47$)	Significance (P-value)
Pulse rate			
> 120/min	12/16 (75%)	9/43 (21%)	< 0.0005
Respiratory rate			
> 30/min	12/12 (100%)	11/42 (26%)	< 0.00001
Urea			
Mean value (mmol/l)	11.7	7.6	< 0.05
Value > 7 mmol/l	12/19 (63%)	19/46 (41%)	NS*
White cell count			
Mean value (x 10^9/l)	13.0	16.1	NS
< 4 or > 20 x 10^9/l	10/18 (56%)	12/42 (29%)	NS
< 4 or > 30 x 10^9/l	6/18 (33%)	1/42 (2%)	< 0.005
Consolidation of lung			
Multilobar	10/19 (53%)	11/47 (23%)	< 0.05
Subclass abnormality			
Any abnormality	9/19 (47%)	22/47 (47%)	NS
Deficient level	3/19 (16%)	6/47 (13%)	NS
Mean values†			NS
Outcome			
Mortality	10/19 (53%)	1/47 (2%)	< 0.00001

* NS = not significant at the 5% level.
† Comparing mean values of IgG1, IgG2, IgG3 and IgG4 between the critically ill and non-severe groups of patients.

Table II. Comparison of IgG subclass levels in critically ill v. less severely ill patients and survivors v. non-survivors

	Community-acquired pneumonia (total of 66 cases)					
Subclass	Normal	High	Low	Normal	High	Low
	Non-severe cases ($N = 47$)			Critically ill ($N = 19$)		
IgG1	35	8	4	12	4	3
IgG2	45	2	0	18	0	1
IgG3	34	11	2	15	4	0
IgG4	47	0	0	16	3	0
	Survivors ($N = 55$)			Non-survivors ($N = 11$)		
IgG1	41	8	6	6	4	1
IgG2	53	2	0	10	0	1
IgG3	40	2	0	9	2	0
IgG4	54	1	0	9	2	0

Abnormalities documented among the IgG subclasses are shown in Table II. Abnormalities of IgG subclasses were found in 20 patients (43%), with no difference relative to the critically ill patients and no apparent association of these abnormalities with any of the other known negative prognostic factors. Complications of illness included renal failure in 3 patients (not requiring dialysis), and jaundice and convulsions in 1 patient each. One patient died.

Combined cases

Pooling of data on all cases allowed comparison of the various parameters indicating severity of pneumonia and the IgG subclass levels between survivors and non-survivors. The results are shown in Table III. A more severe degree of tachycardia, lower mean white cell count and more extreme derangement of white cell count, and a higher mean serum urea level, characterised those patients who died. In addition, more patients who died had a low initial blood pressure. There were no significant differences noted in the number of cases with subclass abnormalities, or in the mean values of the individual subtypes when survivors were compared with non-survivors. There was no apparent association of differences in subclass level and the predictors of outcome when comparing them in survivors and non-survivors. There was also no relationship between complications of illness and abnormalities of subclass levels.

Table III. Differences in clinical and laboratory features of survivors and non-survivors

	Non-survivors (*N* = 11)	Survivors (*N* = 55)	Significance (*P*-value)
Blood pressure			
< 90 mmHg systolic/			
< 60 mmHg diastolic	4/10 (40%)	4/50 (8%)	< 0.05
Pulse rate			
> 120/min	3/8 (38%)	7/51 (14%)	NS*
Respiratory rate			
> 30/min	7/8 (88%)	18/46 (39%)	< 0.05
Urea			
Mean value (mmol/l)	13.3	8.0	< 0.05
Value > 7 mmol/l	7/11 (64%)	24/54 (44%)	NS
White cell count			
Mean value (x 10^9/l)	11.4	16.9	< 0.05
< 4 or > 20 x 10^9/l	4/11 (36%)	18/49 (37%)	NS
< 4 or > 30 x 10^9/l	4/11 (36%)	2/49 (4%)	< 0.01
Consolidation of lung			
Multilobar	5/11 (45%)	16/55 (29%)	NS
Subclass abnormality			
Any abnormality	5/11 (45%)	26/55 (47%)	NS
Deficient level	1/11 (9%)	8/55 (15%)	NS
Mean values†			NS

* NS = not significant at the 5% level.
† Comparing mean values of IgG1, IgG2, IgG3 and IgG4 between the critically ill and non-severe groups of patients.

Discussion

There have been few studies of IgG subclass levels in previously healthy adult patients presenting with an acute episode of community-acquired pneumonia.[5,6]

This study of critically ill patients and less severe cases of community-acquired pneumonia demonstrated a number of differences between these two groups with regard to several parameters that have previously been documented as negative prognostic factors in pneumonia.[7,8] In particular, a greater degree of tachycardia and tachypnoea, extremes of white cell count, higher serum urea concentrations and multilobar pulmonary consolidation characterised the ICU patients (Table I). In addition, while abnormalities in IgG subclass levels (both increased and/or decreased levels) were found in several patients (Table II), there was no significant difference in the occurrence of abnormalities in subtype levels, or of mean levels of the various subtypes, when critically ill and less severe cases of infection were compared. There was also no apparent association between abnormality of subclass levels and either APACHE II score in the ICU patients or, in general, in patients with several of the known poor prognostic factors in pneumonia. Although we had hoped to repeat the measurement of the IgG subclass levels during convalescence in those who survived the pneumonia, particularly those who had initially demonstrated low subtype levels, few patients returned for adequate follow-up. Similarly, when pooling the data and comparing survivors with non-survivors, we noted a number of differences between the groups (Table III).

In reviewing the literature we were able to find only two studies documenting data on IgG subclass levels in previously healthy patients presenting with acute community-acquired pneumonia. A study by Herer and colleagues[5] documented low levels of IgG2 subclass during acute community-acquired pneumonia. Their patients demonstrated persistence of these low levels up to 9 months after the acute infection, but interestingly, these patients responded in a normal fashion to pneumococcal vaccination. A Japanese study[6] documented deficiencies of various IgG subclasses during acute pneumonia, which returned toward normal during convalescence. It was suggested that the low levels that occur during the acute phase of illness may represent 'consumption' of these antibodies during the acute infection. In a study by Soderstrom and colleagues,[9] low levels of IgG subclasses in known deficient patients with a history of recurrent infections were found to be more pronounced during acute episodes of pneumonia as well. In our study a minority of patients had lowered levels of subclasses. Significantly more had elevated levels of various subtypes. Although the experimental design does not allow elucidation of mechanisms of these changes, it is interesting to speculate that they may represent various antibody responses to acute infection.

Our study of cases of acute community-acquired pneumonia suggests that although differences in subclass levels may occur in such patients, these (particularly decreased levels) are relatively infrequent, and we would not routinely test such cases for IgG subclass levels, but confine such testing solely to patients presenting with recurrent infections.

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