Seasonal variation in community-acquired pneumonia

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ABSTRACT: Seasonal variation in the incidence of disease in general, and of infectious diseases in particular, is vitally important information for epidemiologists and for clinicians who deal with these diseases. In relation to community-acquired pneumonia (CAP), the seasonal distribution of the disease and, in particular, of each of the specific aetiological agents is important.

All 346 adult patients who were admitted to a regional hospital in southern Israel for CAP over a period of 1 year were included in a prospective study. As part of the study, a comprehensive diagnostic work-up was performed to identify the specific causative agents for CAP. The study findings were analysed and are presented in terms of the seasonal distribution of the disease.

Thirty four percent of CAP cases occurred in the spring and only 18% in the autumn (p=0.036). Respiratory viruses CAP were predominant in the winter and spring (p=0.009), whilst *Mycoplasma pneumoniae* CAP reached its peak incidence of 41% in the spring compared with 15% during the winter months (p=0.054). No significant seasonal predominance was observed for the other specific aetiological agents of CAP. In 58% of the CAP patients who were hospitalized in the autumn we identified a pneumococcal aetiology, whilst this agent was found in only 32% of the cases in the winter.

In contrast with popular public opinion, winter with its low temperatures is not the main reason for the development of community-acquired pneumonia. Most of the specific aetiologies for community-acquired pneumonia, with the exception of respiratory viruses and *Mycoplasma pneumoniae*, have no seasonal predilection.
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Community-acquired pneumonia (CAP) is a common infectious disease. Like other infectious diseases, its seasonal variation has epidemiological significance. Despite the high prevalence of CAP and the importance of its seasonal distribution, this subject has not been reported often in the literature. Only a minority of studies on CAP have related to the seasonal incidence of the disease [1–3].

In a comprehensive prospective study of 346 adult patients, who were hospitalized with CAP in the Soroka Medical Center in Beer-Sheva, Israel over the course of 1 year, we had the opportunity to determine the seasonal incidence of CAP and of each of its specific aetiological agents. The purpose of this paper is to describe and discuss this seasonal variation.

The Soroka Medical Center in Beer-Sheva is located in a city of 150,000 residents in the south of Israel. It serves a population of 300,000 inhabitants of the Negev region, a semi-arid desert area, mainly at sea level. Average temperatures during the study year ranged from 27°C in the summer to 9°C in the winter. The average yearly rainfall (which falls exclusively during the winter) is 200 mm.

Materials and methods

Patients

We conducted a prospective study of the cause of CAP in 346 adult patients who were admitted to the hospital with this diagnosis at the Soroka Medical Center in Beer-Sheva, Israel over the period of 1 year between November 1, 1991 and October 31, 1992. The study was approved by the review board for human research (the Helsinki committee) of the Soroka Medical Center, and all patients gave their informed consent to participate.

The mean (SD) age of the patients was 49 (20) yrs (range 17–94 yrs). One hundred and eighty seven patients (54%) were male. Sixteen patients (5%) died in the hospital. All other patients were alive at least 6 weeks after admission to the hospital. During the course of their hospitalization, the patients were diagnosed and treated by the medical staff of the internal medicine wards, without intervention by the investigators. At discharge, the patients were referred to the investigators

at the pulmonary disease clinic of the hospital, for clinical and radiological follow-up.

CAP was diagnosed by the presence of an acute febrile disease, with an acute pulmonary infiltrate on chest radiogram, and a clinical and radiological course that confirmed the diagnosis. Exclusion criteria included patients with positive blood tests for human immunodeficiency virus (HIV), patients with lung malignancies, and patients who were discharged from the hospital less than 21 days before their present admission to the hospital with pneumonia.

Causal diagnoses

In addition to routine hospital blood tests (complete blood count, biochemistry and blood cultures), a serum sample was obtained within the first 48 h of admission for serological testing. A second (convalescence) serum was obtained from 308 patients (89%), usually at the follow-up appointment. The mean (SD) interval between the two serum samples was 32 (12) days (range 17–45 days). All sera were separated immediately and stored at -70°C until tested.

The diagnosis of bacterial pathogens was based on positive blood cultures and/or positive serological tests. In patients with a positive blood or pleural fluid culture, the isolated bacterium was considered to be the causative agent of CAP. In order to identify possible bacterial pathogens in patients with negative blood cultures, 308 serum pairs were tested for the presence of specific antibodies to *Streptococcus pneumoniae* pneumolysin, *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis.* Immunoglobulin G (IgG) antibodies to pneumococcal protein toxin, pneumolysin, were measured by enzyme immunoassay (EIA) utilizing pneumolysin produced in *Bacillus subtilis* as antigen [4]. A rise in antibody titre equal to or more than twofold between paired sera was considered diagnostic for S. *pneumoniae* infection [4, 5]. Total antibodies to unencapsulated *H. influenzae* [6] and *M. catarrhalis* [7, 8] were measured by EIA, using whole bacterial cells of respective bacteria as antigens. A rise in antibody titre of ≥3 between paired sera was considered to be diagnostic.

S. pneumoniae specific immune complexes were determined in all 654 (paired and unpaired) sera, by measuring antibodies to pneumolysin and to the mixture of 23 capsular polysaccharides present in vaccine, from precipitated and redissolved immune complexes [9, 10]. The cut-off value for the presence of *S. pneumoniae* immune complexes was based on results of serum samples from 40 healthy elderly people (mean±2 SD). All bacterial serological tests were conducted at the Finnish National Public Health Institute in Helsinki and in Oulu, Finland.

CAP was considered to be caused by *S. pneumoniae* if there was a positive culture for *S. pneumoniae* (blood or pleural fluid), or a positive serological diagnosis for *S. pneumoniae* based on pneumolysin antibodies or the presence of *S. pneumoniae* specific immune complexes, as detailed above. CAP was determined to be caused by *H. influenzae* or *M. catarrhalis* in the presence of a positive blood culture or positive serology.

Serological testing was used to identify *Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella* spp.,

Coxiella burnetti and six respiratory viruses (influenza A, influenza B, adenovirus, respiratory syncytial virus (RSV), parainfluenza 1 and parainfluenza 3). Details of the various serological methods used and of the criteria for positive serological diagnoses for each of these causative agents have been published previously [11].

Meteorological data

Measurements of mean daily temperatures and relative humidities for the study months were conducted at the Beer-Sheva meteorological station of the meteorological service of the Israel Ministry of Transportation.

Data analysis

The date of hospitalization was used as the time of occurrence of pneumonia in this study. To analyse the seasonal incidence of CAP, the months of September, October and November were defined as autumn, December, January and February as winter, March, April and May as spring, and June, July and August as summer. The Chi-squared test was used to determine the significance of differences in incidence between the seasons. The null hypothesis of the study was that there were no seasonal differences in the incidence of CAP. A p-value of <0.05 was considered significant.

Results

Table 1 shows the frequency distribution of the various causal agents for CAP among the 346 patients hospitalized with this diagnosis during the course of the study year. In all, the causal agent was identified in 279 patients (81%). A single aetiology was found in 146 patients (42%), while more than one aetiological agent was found in 133 patients (38%).

The aetiological frequencies by age and a discussion of the incidence of multiple aetiologies for CAP can be found in our previous publication on these subjects [11].

Table 1. – Frequency distribution of community-acquired pneumonia (CAP) aetiologies in 346 patients

Pathogen	Patients	
	n	%
Pneumococcus	148	43
Mycoplasma pneumoniae	101	29
Chlamydia pneumoniae	62	18
Legionella spp.	56	16
Viruses	35	10
Coxiella burnetii	20	6
Haemophilus influenzae	19	6
Other*	21	6
Unknown aetiology	67	19

*Including *Moraxella catarrhalis* (7), active pulmonary tuberculosis (7), nonpneumoniae streptococcus (4), *Staphylococcus aureus* (1), *Acinetobacter* spp. (1), and *Pseudomonas aeruginosa* (1).
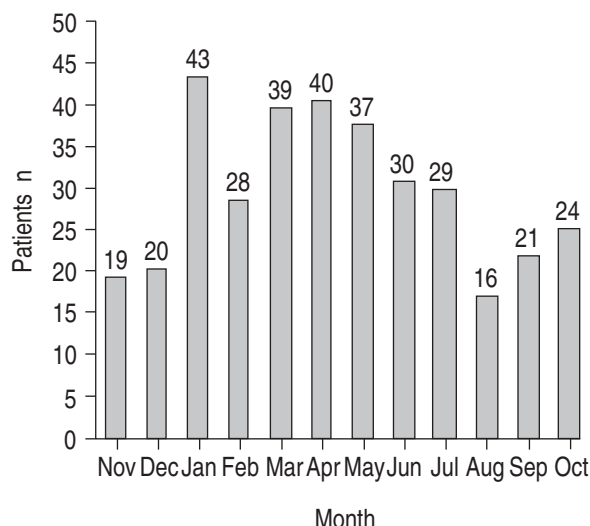
Fig. 1. – The distribution of total community-acquired pnuemonia (CAP) by months of the year.

Figure 1 shows the distribution of all CAP patients by month of the year. The peak month of hospitalization for CAP was January; August had the fewest admissions. The months from March until May had relatively high rates of CAP admissions.

Table 2 shows the frequency distribution of CAP and its primary aetiologies by season. Thirty four percent of the cases occurred in the spring, while only 18% were seen in the autumn (p=0.036). Viral aetiology was particularly prevalent in the winter and spring (49 and 37%, respectively), with relatively low incidence in the summer and autumn (p=0.009). Forty one percent of the cases of *M. pneumoniae* CAP occurred in the spring compared to 15% during the winter months. These seasonal differences for *M. pneumoniae* reached borderline statistical significance (p=0.054). Other aetiological agents such as *S. pneumoniae, C. pneumoniae, Legionella* spp., and cases of unknown aetiology did not show significant seasonal variation in their incidence.

Table 3 shows the relative incidence of CAP by aetiology and season. Because of the high rate of multiple

Table 2. – Frequency distribution of total community-acquired pneumonia (CAP) and its aetiologies by seasons

	n	Autumn %	Winter %	Spring %	Summer %	p-value*
Total CAP	346	18	26	34	22	0.036
Pneumococcus	148	25	20	34	21	0.292
Mycoplasma pneumoniae	101	19	15	41	25	0.054
Chlamydia pneumoniae	62	18	29	27	26	0.798
Legionella spp.	56	27	21	21	30	0.888
Respiratory viruses	35	3	49	37	11	0.009
Unknown aetiology	67	18	33	33	16	0.331

*the p-value comparing the observed seasonal distribution of CAP and each of these aetiologies, with an expected equal seasonal distribution, by Chi-squared test.

Table 3. – Relative incidence of aetiologies of comunity-acquired pneumonia (CAP) as a percentage of total CAP, by seasons*

	Autumn (n=64) %	Winter (n=91) %	Spring (n=116) %	Summer (n=75) %
Pneumococcus	58	32	44	41
Mycoplasma pneumoniae	30	16	36	33
Chlamydia pneumoniae	17	20	15	21
Legionella spp.	23	13	10	23
Respiratory viruses	2	19	11	5
Unknown aetiology	19	24	19	15

*the sum of percentages for each of the columns is greater than 100% since some of the patients had multiple aetiologies for CAP.

Table 4. – Mean daily temperatures and relative humidity in Beer-Sheva, Israel during the months of the study

Month	Mean daily temperature °C	Mean daily relative humidity %
November 1991	17.9	62.7
December 1991	11.1	66.5
January 1992	9.0	68.0
February 1992	9.7	71.5
March 1992	12.8	60.6
April 1992	17.4	56.4
May 1992	21.6	51.2
June 1992	24.9	49.2
July 1992	25.6	55.3
August 1992	27.1	58.9
September 1992	24.5	57.9
October 1992	23.0	59.3

aetiologies, we could not conduct a statistical comparison of seasonal incidence. This also explains why the sum of the percentages is greater than 100% for each season. It is noteworthy that in the autumn pneumococcal CAP was identified in 58% of the CAP patients, while this aetiology was found in only 32% of the patients admitted in the winter. *M. pneumoniae* was found in only 16% of the patients diagnosed in the winter. Respiratory viruses were identified in only 2 and 5% of CAP patients in the autumn and summer, respectively, compared with 19 and 11% of patients in the winter and spring, respectively.

Table 4 presents data relating to mean daily temperatures and relative humidities in Beer-Sheva during the months the study was conducted.

Discussion

The seasonal distribution of CAP and the seasonal variation of its aetiological agents, as found in the present study, have three unique features which raise questions as to the general validity of our findings: the CAP patients were all hospitalized; the study was conducted over one year only; and the geographical region is limited. The majority of published studies on CAP, like our own, have reported only on hospitalized patients. Data on CAP patients who were not hospitalized

is scarce. In retrospect, many of the patients in the present study did not have a clear-cut indication for hospitalization [12]. In this respect, our results also reflect, at least in part, the distribution of nonhospitalized CAP patients.

This study lasted for 1 year, a period of time which enabled us to present the seasonal incidence of CAP and its main aetiologies for that year. An important question is whether the findings of that particular year are representative of other years. Two studies that reported on the incidence of CAP over consecutive years [1, 3] showed that peak seasonal incidences are not identical from year to year. These reports oblige us to qualify the generalizability of our data with the statement that the seasonal distribution presented is valid for the study year itself and may not indicate similar incidences for other years.

As the present study was limited to one year, we cannot definitively confirm or negate the possibility that the study period represented an "epidemic period" for at least some of the pathogens. Although analysis of the monthly frequency distribution of each of the aetiological agents negates the possibility that an epidemic lasted for the entire year, it is conceivable that these distributions reflect epidemics lasting for several years, with seasonal outbreaks in certain seasons during each of the epidemic years. This question might have been more effectively addressed, particularly for *M. pneumoniae,* if we had been able to test sera of other populations, that did not have CAP, from this same time period. Unfortunately, such sera was not available to us for testing.

The geographical region in which this study was conducted, *i.e.* the south of Israel, could also affect the generalizability of our findings, in light of the regional variation which has been reported in the prevalence of various CAP pathogens [11]. The climate in the Negev region of southern Israel is relatively hotter than many other regions of the western world, and could affect the seasonal distribution of CAP as reported here.

Despite the fact that the prevalence of all cases of CAP reached a peak in January, the incidence of CAP in the winter was only 26% of the rate for the entire year. On the other hand, each of the spring months (March to May) showed relatively high rates of total CAP, so that the incidence of CAP in the spring reached 34% of the year's incidence. In contrast, each of the monthly incidences in the autumn were relatively low, and the total incidence for this season was only 18%. These seasonal differences were statistically significant. We conclude from these findings and from the meteorological data presented in table 4 that, in contrast with the popularly held view of the general public, the winter with its low temperatures and high humidity is not the main cause of CAP. Similarly, the seasonal incidence found by us does not support the contention that the transition months are "risk periods" for CAP, as they are for allergic disorders, since a particularly low incidence of CAP was found in the autumn. We do not have a convincing explanation for the peak prevalence of CAP in the spring. The meteorological data do not provide an explanation for this peak. The possibility that an epidemic peak of one of the aetiological agents caused the observed peak for all CAP

pathogens is not logical, since all the pathogens demonstrated a clear increase in prevalence in the spring months.

MARRIE *et al.* [2] described 588 CAP patients who were hospitalized over a period of 5 yrs. Analysis of the pooled monthly distribution of cases for the entire study period shows that the seasonal frequencies were almost equal. FRANSEN [3], on the other hand, reports the number of hospitalizations by month for each of the 3 study years. The peak of hospitalizations for CAP was in the spring in 1964, in the late spring and early summer in 1965, and in the winter in 1966. FOY *et al.* [1] reported the incidence of "total pneumonia" over a consecutive 5 year period. Their report was not restricted to hospitalized patients or to adults. Three of the annual peaks in this report occurred in the spring and two other peaks occurred in the winter. We believe that these series show that there is a seasonal variation in the incidence of total CAP and that in the majority of cases the peak incidence occurs in the spring months, as we also found, although some peaks are also observed in the winter months.

The six respiratory viruses that we investigated as causative agents for CAP had significantly higher incidence in the winter and spring, a low incidence in the summer, and were almost not found in the autumn. This is consistent with data showing that influenza A and influenza B, which caused most of the respiratory viral infections in the present study, reach peak incidence in the winter and spring [13].

The occurrence of *M. pneumoniae* CAP throughout the year is a well-documented finding in the literature [1, 14–20]. Seasonal peaks have been reported in only some of these studies. These peaks have been reported in varying periods ranging from the end of summer to winter [14, 16–20]. In the present study, we observed a seasonal peak (with borderline statistical significance) in the spring, with a gradually decreasing incidence as winter approached. The early appearance of a seasonal peak in this study may be due primarily to the relatively warm climate in our region, which is reflected in mean temperatures in the spring which are similar to those measured in the summer months in regions of the world in which the peak occurrence of CAP has been reported to be in the summer.

There was a higher, though not statistically significant, incidence of pneumococcal CAP in the spring compared to the other seasons of the year. This incidence is similar to the higher incidence of pneumococcal infections in the spring observed by FRANSEN [3].

Two important causative agents of CAP, *Legionella* spp. and *C. pneumoniae* had equal distributions of CAP incidence throughout the year. This is consistent with previous reports concerning CAP caused by *C. pneumoniae* [21, 22] and *Legionella* spp. [23, 24].

From the point of view of the clinician responsible for the treatment of CAP patients, the seasonal variation of CAP as presented in table 3 (*i.e.*, the relative incidence for each specific aetiology by season) is important. In this method of presentation, one can see that in certain seasons of the year the relative incidence of specific aetiologies is as much as 2 times higher than in other seasons. However, it is difficult to think of practical applications for this method of presentation,

since the specific frequency for each of the aetiologies is large enough to necessitate appropriate antibiotic therapy at least in the first stage of treatment, considering the large degree of overlap in the clinical manifestations of the various aetiologies of CAP [25].

We conclude that, despite prevailing popular opinion, winter with its low temperatures is not the main explanation for the incidence of community-acquired pneumonia. Specific aetiological causes of community-acquired pneumonia, with the exception of respiratory viruses and *Chlamydia pneumoniae,* do not show significant seasonal variation.

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