

## Increased risk of invasive pneumococcal disease in haematological and solid-organ malignancies

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### SUMMARY

Large-scale population-based studies have reported a significant increase in invasive pneumococcal disease (IPD) in those with underlying haematological or solid-organ malignancy, but limited condition-specific data are available on rates of IPD in the adult population. A retrospective chart review of all patients with IPD (identified prospectively) in the province of Alberta, Canada (population ~3·3 million) was conducted from 2000 to 2004 to study the epidemiology of IPD. Rates of IPD in patients with various haematological and solid-organ malignancies were determined by obtaining the number of these patients at risk from the provincial cancer registry. Compared to the attack rate of IPD in the adult population aged  $\geq 18$  years (11·0 cases/100 000 per year, 95% CI 10·44–11·65), there were significantly increased rates of IPD in those with lung cancer (143·6 cases/100 000 per year, OR 13·4, 95% CI 9·3–19·4,  $P < 0\cdot001$ ) and multiple myeloma (673·9 cases/100 000 per year, OR 62·8, 95% CI 39·6–99·8,  $P < 0\cdot001$ ). More modestly increased rates of IPD were found in those with chronic lymphocytic leukaemia, acute myeloid leukaemia, acute lymphoblastic leukaemia, and Hodgkin's and non-Hodgkin's lymphoma. There was an increased prevalence of serotype 6A in those with these underlying malignancies, but no other serotypes predominated. Fifty-three percent (48/83) of cases were caused by serotypes in the investigational 13-valent pneumococcal conjugate vaccine (PCV13), and 57/83 (69%) of the cases were caused by serotypes in the 23-valent pneumococcal polysaccharide vaccine (PPV23). The incidence of IPD in adults with certain haematological and solid-organ malignancies is significantly greater than the overall adult population. Such patients should be routinely given pneumococcal polysaccharide vaccine; this population could also be targeted for an expanded valency conjugate vaccine.

**Key words:** Invasive pneumococcal disease, malignancy, pneumococcus, serotype, vaccine.

### INTRODUCTION

*Streptococcus pneumoniae* is an important cause of community-acquired pneumonia, bacteraemia, and

meningitis. Invasive pneumococcal disease (IPD) is defined as isolation of *S. pneumoniae* from a normally sterile body site (typically blood or cerebrospinal fluid), and carries with it significant morbidity and

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mortality, even in the modern antibiotic era. The mortality rate of pneumococcal bacteraemia in a large prospective international study was 16.9% in those with age >65 years and the presence of underlying disease or risk factors for immunosuppression significantly associated with increased mortality [1]. Pneumococcal meningitis also leads to poor outcomes, carrying a mortality rate of 21% [2]. Various states of immunodeficiency, including underlying malignancy, are recognized as risk factors for IPD [3, 4]. Vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPV23) is efficacious against IPD and recommended for patients in high-risk groups, including all patients with malignancy [5–7]. Unfortunately, many patients with IPD who have an indication for vaccination are not vaccinated despite multiple encounters with the healthcare system [8].

Large-scale population studies have found increased rates of IPD in paediatric and adult patients with haematological and solid-organ malignancies [9–11], but condition-specific data is lacking. We conducted a large 5-year retrospective study of all adult patients aged  $\geq 18$  years with IPD in the province of Alberta and obtained provincial prevalence data for various malignancies from the Alberta Cancer Board to determine the rates of IPD in patients with selected underlying malignancies.

## METHODS

### Demographics and definitions

The study was conducted in the province of Alberta from 2000 to 2004, which at the time of the study was divided into nine health regions. The population was 2 967 755 in 2000 and 3 179 036 in 2004 [12]. Cases of IPD were defined as the isolation of *S. pneumoniae* from any normally sterile body site, including blood, cerebrospinal fluid, pleural fluid, biopsy tissue, synovial fluid, pericardial fluid, and peritoneal fluid [13]. In Alberta, IPD is a notifiable disease reportable to the Provincial Health Office. *S. pneumoniae* isolates recovered from patients with IPD are submitted to the National Centre for Streptococcus (NCS) located in Edmonton, Alberta, for capsular serotyping and antimicrobial resistance profiling for trending analysis. Isolates were submitted to the NCS prospectively from acute diagnostic microbiology laboratories in Alberta during the study period.

To ensure as complete as possible the capture of all patients with IPD in Alberta during the study period,

a number of databases were utilized. These included all patients identified by identification of *S. pneumoniae* isolates sent to the NCS, all patients reported to the provincial health office, and all patients captured in both the Calgary area *S. pneumoniae* Research Group database (Calgary, AB) and the Community Acquired Pneumonia Study database (Edmonton, AB). All four databases were combined to form the final dataset, and duplicate patients (identified by personal health number) were counted only once. An extensive retrospective chart review of all identified patients was then performed for all identified IPD cases occurring during the survey period. Current underlying malignancies were recorded as described in the chart. Haematological malignancies were defined as any leukaemia, any lymphoma, or multiple myeloma.

In the laboratory, upon receipt of *S. pneumoniae* isolates, bacteria were stored at  $-70^{\circ}\text{C}$  until serotyping and susceptibility assays were performed. Only one isolate from each IPD case was included in the review unless the isolates were collected  $\geq 1$  month apart or were of a different serotype if  $< 1$  month had elapsed between episodes of IPD.

Annual incidence rates of IPD for the general population were calculated between 2000 and 2004 using provincial population estimates from Alberta Health and Wellness [12]. Condition-specific incidence rates of IPD between 2000 and 2004 were calculated based on annual prevalence data of haematological and solid-organ malignancies obtained from the provincial cancer registry, maintained by the Alberta Cancer Board [14]. The registry records all new cancer cases throughout the province and also tracks all cancer-related deaths using information from Alberta Vital Statistics and Statistics Canada. Malignancies considered in our study included lung cancer (small-cell and non small-cell), multiple myeloma, chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), Hodgkin's lymphoma, and non-Hodgkin's lymphoma.

The study received approval from the institutional research review committees of all nine health regions in Alberta and also from the University of Alberta and the University of Calgary.

### Serotyping of *S. pneumoniae* isolates

Isolates received at the NCS were confirmed as *S. pneumoniae* based on morphology and optochin

Table 1. Rates of invasive pneumococcal disease (IPD) in patients with underlying malignancy, 2000–2004

Malignancy	IPD cases 2000–2004/cases of specified malignancy	Incidence rate/100 000 per year (95% CI)	OR (95% CI) compared to general population	P value (two-tailed Fisher's exact test)
Lung cancer	29/20 198	143.6 (91.36–195.80)	13.41 (9.30–19.35)	<0.001
Multiple myeloma	18/2671	673.9 (363.63–984.18)	62.83 (39.56–99.80)	<0.001
Chronic lymphocytic leukaemia	11/8039	124.4 (47.34–201.45)	12.61 (7.02–22.65)	<0.001
Acute myeloid leukaemia or acute lymphoblastic leukaemia	10/7740	129.2 (49.17–209.23)	11.90 (6.45–21.97)	<0.001
Hodgkin's lymphoma	4/8383	47.8 (0.97–94.47)	4.37 (1.70–11.26)	0.014
Non-Hodgkin's lymphoma	12/18 905	63.5 (27.57–99.38)	5.846 (3.34–10.25)	<0.001

OR, Odds ratio; CI, confidence interval.

susceptibility [15]. Serotyping was performed at the NCS by Quellung reaction using commercial antisera prepared at the World Health Organization (WHO) Collaborating Center for Reference and Research on Pneumococci, located at the Statens Serum Institut Copenhagen, Denmark [16]. Strains that failed to type were confirmed as *S. pneumoniae* using Accuprobe™ (Genprobe, USA).

### Statistical analysis

Incidence rates and serotype prevalence were compared between various malignancies and the general adult population (all adults aged  $\geq 18$  years) using Fisher's exact test. All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., USA).

## RESULTS

### Incidence rates of IPD for patients with various malignancies vs. general population

A total of 1768 cases of IPD were identified in Alberta between 2000 and 2004 for which laboratory and clinical data were both complete. Of these cases 1273 occurred in patients aged  $\geq 18$  years, for an incidence rate of 11.0 cases/100 000 population per year (95% CI 10.44–11.65). Of these, 152 (11.9%) cases occurred in adult patients with some form of underlying malignancy. Sixty-one (4.8%) cases involved patients with an underlying haematological malignancy, 82 (6.4%) cases involved patients with an underlying solid-organ malignancy (including cutaneous malignancies), and four (0.3%) occurred in patients who had haematological and solid-organ malignancies together. In the remaining five (0.4%) cases, the

underlying malignancy was not classifiable based on the information in the database.

None of the four patients with haematological and solid-organ malignancies occurring together had lung cancer, hence these patients were grouped with their respective haematological malignancy in the final condition-specific analysis. Ten patients with haematological malignancy (six with lymphoma, four with leukaemia) were not able to be classified further based on information available from the database – these patients were not included in the condition-specific analysis. In total, 84 cases were included in the final condition-specific analysis, comprised of 29 patients with lung cancer and 55 patients with classifiable haematological malignancy.

The condition-specific incidence rates of IPD identified during the study period are given in Table 1 and compared to rates of IPD in the general adult population aged  $\geq 18$  years. There was an increased risk of IPD in all six malignancies compared to the remainder of the general adult population aged  $\geq 18$  years. With respect to the haematological malignancies, the risk of IPD steadily increased from patients with lymphoma (4.4 times greater with Hodgkin's, 5.8 times greater with non-Hodgkin's) to leukaemia (11.9 times greater with AML or ALL, 12.6 times greater with CLL), and was highest in those with multiple myeloma (62.8 times greater). There was a 13.4 times greater risk of IPD in those with lung cancer.

### Pooled analysis of haematological malignancies including unclassified cases

Given the number of unclassified haematological malignancies not included in the condition-specific

Table 2. Analysis of rates of invasive pneumococcal disease (IPD) in patients with haematological malignancies (including patients with unclassified haematological malignancies), 2000–2004

Malignancy	IPD cases 2000–2004/cases of specified malignancy	Incidence rate/100 000 per year (95% CI)	OR (95% CI) compared to general population	P value (two-tailed Fisher's exact test)
Any lymphoma	22/27 288	80.6 (46.95–114.3)	7.48 (4.92–11.37)	<0.001
Any leukaemia	25/15 779	158.4 (96.38–220.5)	14.76 (9.96–21.88)	<0.001
Any haematological malignancy	65/45 738	142.1 (107.59–176.64)	13.64 (10.63–17.50)	<0.001

OR, Odds ratio; CI, confidence interval.

analysis, we performed a pooled analysis which included these cases. Table 2 gives the results of a pooled analysis of all cases of lymphoma and leukaemia, including the 10 unclassified cases described above, as well as of all haematological malignancies together. The risk of IPD with any lymphoma was 7.5 times greater than the remainder of the general population aged  $\geq 18$  years, which increased to 14.7 times greater with any leukaemia. A pooled analysis of all haematological malignancies including the 10 unclassifiable cases revealed an overall incidence rate of 142.1 cases/100 000 per year (95% CI 107.59–176.64), for a 13.6 times increased risk of IPD compared to the remainder of the adult population aged  $\geq 18$  years (95% CI 10.63–17.50,  $P < 0.001$ ).

#### Demographic and clinical characteristics of patients with IPD and underlying malignancy

Selected demographic and clinical characteristics on the IPD cases in patients with underlying malignancy are provided in Table 3, organized by malignancy. Unclassified cases of lymphoma (six patients) and leukaemia (four patients) were also included. There were 26/29 (90%) patients with lung cancer and IPD that had a history of smoking, but in none of the other malignancies did rates of smoking exceed that of the general population aged  $\geq 18$  years with IPD. Smoking history was not available in 19 cases. Eighty-five of the 94 (90%) patients had pneumococcal bacteraemia, eight had *S. pneumoniae* isolated from pleural fluid, and one had meningitis. Eighty-three of the 94 (88%) patients required admission to hospital, 10 of whom required admission to either an intensive care unit or coronary care unit setting, with the remaining 73 being admitted to a medical or surgical unit. Twenty-six of the 83 (31%) patients admitted to hospital died, with 20 (24%) of these

cases being directly attributed to IPD or complications thereof. The remaining six patients who died were listed in the database as having died of other causes.

#### *S. pneumoniae* serotypes of isolates from cases of IPD with underlying malignancy

There was an increased prevalence of serotype 6A (11/84; 13% vs. 48/1273, 4%, OR 4.7, 95% CI 2.3–9.5,  $P < 0.001$ ) compared to the general adult population aged  $\geq 18$  years, but no other serotypes predominated. Six cases were caused by serotype 9V and five cases by each of serotypes 3, 4, 6B, 19F, and 23F. Four cases were caused by each of serotypes 8, 22F, and 35B. Two cases were caused by each of serotypes 9N, 10A, 11A, 12F, 18C, 23A, 33F, and 38. A single case was caused by each of serotypes 1, 7F, 9L, 13, 14, 15A, 15B, 15C, 17F, 19A, 23B, and 35A. Serotype data was not available in two cases.

Twenty-nine (35%) cases were caused by serotypes in the 7-valent conjugate vaccine (PCV7, Prevnar<sup>®</sup>, Wyeth, USA), 31 (37%) cases were caused by serotypes in the 10-valent conjugate vaccine (PCV10, Synflorix<sup>®</sup>, GlaxoSmithKline, USA) and 48 (57%) cases were caused by serotypes in the 13-valent conjugate vaccine (PCV13, Prevnar 13). Fifty-seven (69%) cases were caused by serotypes in the 23-valent polysaccharide vaccine (PPV23, Pneumovax<sup>®</sup> 23, Merck, USA).

#### DISCUSSION

A 2005 study from the USA estimated the incidence of IPD in patients with haematological malignancy at 503.1 cases/100 000 per year (95% CI 272.6–334.6) and for solid-organ malignancy at 300.4 cases/100 000 per year (95% CI 422.2–622.3). There was a

Table 3. Selected demographic and clinical characteristics of patients with invasive pneumococcal disease (IPD) and underlying malignancy

Characteristic	Lung cancer (n = 29)	Lymphoma* (n = 22)	Leukaemia* (n = 25)	Multiple myeloma (n = 18)
Median age, years (range)	64 (30–88)	60 (24–90)	60 (19–81)	70 (56–82)
Gender (male/female)	16/13	10/12	17/8	11/7
Smoker (current/former/never/ unknown)	15/11/3/0	2/6/9/5	1/6/9/9	4/5/4/5
Source of isolate				
Bacteraemia	24	20	23	18
Pleural fluid	5	1	2	0
Cerebrospinal fluid	0	1	0	0
Hospitalization				
Medical/surgical unit	23	14	23	13
ICU/CCU	3	4	0	3
Emergency room only	2	4	2	0
Outpatient only	1	0	0	2
Mean time in hospital (days)	11.5	20.8	9.2	17.9
≤ 7 days	13	6	17	8
7.1–28 days	10	7	4	3
> 28 days	3	5	2	5
Range (days)	0–59	0–96	0–53	0–95
In-hospital mortality, n (%)	10 (34%)	5 (23%)	6 (24%)	5 (28%)
Died of IPD or complications	7	4	4	5
Died of other causes	3	1	2	0

ICU/CCU, Intensive care unit/coronary care unit.

\* Unclassified cases of lymphoma and leukaemia were included.

38.3 times greater risk for patients with haematological malignancy and a 22.9 times greater risk for those with solid-organ malignancy compared to that of healthy adults [9]. Data from Scotland revealed increased rates of IPD in patients with haematological malignancy (733.7 cases/100 000 per year) and non-haematological malignancy (216.1 cases/100 000 per year) [10]. Data on the incidence of IPD in adults with specific underlying malignancies is limited, although a recent study from Germany found a 10 times greater risk of IPD in children with ALL [17].

In our 5-year retrospective analysis, we identified 29 cases of IPD in patients with lung cancer in the province of Alberta between 2000 and 2004, a 13.4 times greater incidence of IPD compared to the remainder of the adult population aged  $\geq 18$  years. If lung cancer is considered a surrogate for solid-organ malignancy, the incidence rate and odds ratio calculated in our study are lower than results previously estimated for solid-organ malignancies [9, 10].

In our study, the highest rates of IPD were found in patients with multiple myeloma, who had a 62.8 times greater risk compared to the remainder of the general

population aged  $\geq 18$  years. Patients with multiple myeloma have been well-described as being at increased risk of bacterial infections with both Gram-positive and Gram-negative organisms, although the reasons for this have not been clearly elucidated [18]. Multiple myeloma leads to defects in complement activation and neutrophil function, as well as functional hypogammaglobulinaemia [19]. Decreased CD4 counts and decreased CD4/CD8 ratios have also been found in patients with multiple myeloma [20]. More modestly increased rates of IPD were found in patients with other haematological malignancies including lymphoma, CLL, and AML/ALL. The overall rate in patients with underlying haematological malignancy of 142.1 cases/100 000 per year is less than has been previously reported [9, 10].

Serotype 6A, which was the only serotype to have an increased prevalence compared to the general adult population, is one of the six serotypes included in PCV13 but not in PCV7 or PCV10. Overall, 19/152 (12.5%) cases of IPD in patients with underlying malignancy were caused by one of the six serotypes included in PCV13 but not PCV7 or PCV10. The use

of PCV13 directly in this high-risk population as well as in children may confer beneficial protective effects against IPD in patients with underlying malignancy via both direct and indirect ('herd') effects [21].

There are limitations to our study. We only captured patients with a positive isolate, and it is possible that cases of IPD were missed if cultures were not done or if they were negative (e.g. if drawn after the administration of antibiotics). Mortality rates reflect patients who died in hospital only. We relied on documentation of malignancy on the patient's chart, and it is possible that cases were missed because a patient's medical history was not documented. In some cases not enough detail was provided in the chart (i.e. only 'lymphoma' or 'leukaemia' were reported) to classify patients into the appropriate condition-specific groups for analysis. Hence, our study provides a minimal estimate of the risk of IPD and the actual risk may be higher. Pneumococcal vaccination status of patients could not be accounted for in our study. Age and smoking status may have confounded results, as may have other factors not accounted for in this study.

Our study reinforces that the risk of IPD is significantly increased in lung cancer and various haematological malignancies, and a systemic PPV23 vaccination strategy among those providers who care for these patients should be considered. Evaluation of an expanded valency conjugate vaccine in this high-risk population via prospective studies is warranted.

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#### DECLARATION OF INTEREST

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