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Asplenic patients and invasive pneumococcal disease—how bad is it these days?

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SUMMARY

Objectives: Most are aware of pneumococcal infection as a complication of splenectomy and the increased risk of severe invasive pneumococcal disease (IPD) in asplenic patients. However little is known of the current status of this entity in a population with an active pneumococcal conjugate vaccine program for children.
Methods: All IPD cases reported from 2000 to 2014 in Northern Alberta, Canada were collected prospectively. Socio-demographic variables, clinical characteristics, and IPD-related outcomes were compared between patients with and without a spleen using the Student *t*-test, Chi-square test, or Fisher's exact test, as appropriate.
Results: Thirty-seven of 2435 patients with IPD (1.5%) were asplenic. Asplenic patients were significantly more likely to require mechanical ventilation or admission to the intensive care unit and had more complications (e.g., acute kidney injury). However, in-hospital mortality rates were similar in those with and without a spleen (19% vs. 16%, $p = 0.58$). Pneumococcal serotype 22B was 33-fold higher in asplenic patients compared to those with a spleen.
Conclusions: In patients with IPD, those who are asplenic have a more severe infection than those with a spleen; however, the mortality rate is not significantly different. The reason for the predominance of serotype 22B requires further investigation and if replicated may warrant attention to current vaccination strategies.

1. Introduction

Splenic macrophages remove poorly opsonized bacteria (those that are encapsulated, like *Streptococcus pneumoniae*) from the blood stream very efficiently.[1] In addition, the spleen is the major site of synthesis of immunoglobulin M and opsonins such as tuftsin and properidin.[1] It is no surprise then that overwhelming pneumococcal sepsis can occur in splenectomized patients.[2,3] While encapsulated microorganisms other than *S. pneumoniae* can cause bacteremia in splenectomized persons, in a study of 52 asplenic patients with sepsis compared with 52 septic patients with their spleens, *S. pneumoniae* was more frequently detected amongst the asplenic group (42% vs. 12%), whilst the rate of Gram-negative sepsis was similar in the two groups.[4]

There is very little current information on the extent and nature of the problem of pneumococcal sepsis in the asplenic patient, and splenectomy itself is not uncommon. In Alberta, Canada, approximately 150 splenectomies are performed each year (Li Huang, Alberta Health Services, personal communication). Conjugated pneumococcal vaccines have been used in Alberta since the early 2000s. The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced for children in Alberta in 2002 and the 13-valent pneumococcal vaccine (PCV13) in 2010. There is a standardized clinical policy that all patients receive pneumococcal, meningococcal, and *Haemophilus influenzae* vaccines either prior to splenectomy, if possible, or prior to hospital discharge post splenectomy.

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Thus, it was sought to determine the effect of asplenia on the manifestations and outcomes of invasive pneumococcal disease (IPD). This study formed part of a prospective 15-year study of IPD in Northern Alberta, Canada.

2. Methods

2.1. Definitions

Cases of IPD were defined as per the Alberta Health Public Health Notifiable Disease Management Guidelines (http://www.health.alberta.ca/documents/ Guidelines-Pneumococcal-Disease-Invasive-IPD-2011).[5] Pneumococcal isolates from cases of invasive disease were collected from normally sterile sites defined as blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, bone, joint or specimens taken during surgery. As per the aforementioned guidelines, all IPD isolates were submitted to the Provincial Laboratory for Public Health (PLPH) located in Edmonton, Alberta for capsular serotyping.

2.2. Clinical data collection

Cases of IPD were identified through an isolate database housed at the PLPH. An IPD case list was generated. Research nurses retrospectively collected clinical data for each case using this list. Socio-demographic, clinical, functional, and laboratory data were collected using a standardized case report form (CRF). From 2000 to 2014, data were collected on all patients in Northern Alberta with IPD (approximate population 2 060 039). The research nurses received training on data collection prior to the start of the study. In addition to the CRF, standard operating procedures documents, definitions, drug classification, and underlying illness categorization were part of their working documents. With respect to underlying illnesses, if the attending physician recorded such an illness it was accepted as such for the purpose of the study. Acute kidney failure was specifically defined as an absolute increase in serum creatinine of 100 mmol/l over the baseline creatinine, or any requirement for dialysis. This study received approval from the institutional research review committees of all Northern Alberta health regions, as well as the University of Alberta ethics review board.

2.3. Identification and serotyping of S. pneumoniae isolates

S. pneumoniae isolates were received at the PLPH from acute diagnostic laboratories in Alberta, as per the requirements of the provincial notifiable disease guidelines. *S. pneumoniae* isolates were confirmed as *S. pneumoniae* based on characteristic morphology and optochin susceptibility prior to serotyping.[6] All pneumococcal isolates that exhibited a positive Quellung reaction using commercial type-specific antisera obtained from Statens Serum Institute, Copenhagen, Denmark were assigned a serotype designation.[7]

2.4. Exposures and outcomes

The independent variable of interest was asplenia; it was specifically asked whether the patient had undergone a splenectomy, and patients were categorized into those with or without a spleen based on these data. Patients who had a spleen were classified into the spleen group regardless of spleen function. The primary outcomes of interest were the occurrence of major in-hospital complications defined as the presence of cellulitis, osteomyelitis, septic arthritis, meningitis, admission to the intensive care unit (ICU), need for mechanical ventilation, acute kidney injury, and all-cause in-hospital mortality. In addition, serotyping of all isolates was performed and the results were stratified and described according to the presence or absence of a spleen.

2.5. Statistical analysis

The analyses were largely descriptive in nature. Socio-demographic variables, clinical characteristics, and IPD-related outcomes were compared between patients with and without a spleen using the Student *t*-test, Chi-square test, or Fisher's exact test, as appropriate. All analyses were performed with Stata SE, version 12.1 (Stata, College Station, TX, USA).

3. Results

3.1. General description

Thirty-seven (1.5%) of the 2435 patients identified with IPD in the study were asplenic. Table 1 provides a comparison of IPD patients who were asplenic and those who were not. Patients who were identified as asplenic were more likely to be living at home ($p = 0.026$) and to have had a solid tumor cancer within the past 5 years ($p < 0.001$). They were, however, less likely to be aboriginal ($p = 0.011$), have alcoholism ($p = 0.039$), or use illicit drugs ($p = 0.006$), and were less likely to have chronic obstructive pulmonary disease ($p = 0.13$).

3.2. Outcomes according to the presence or absence of a spleen

Table 2 shows the pre-specified outcomes stratified according to the presence or absence of a spleen. Those without a spleen had a more severe infection as measured by markers of supportive treatment intensity, such as the need for mechanical ventilation ($p = 0.008$) and ICU admission ($p = 0.001$). They were also more likely to have complications of pneumococcal bacteremia such as meningitis ($p < 0.001$), as well as complications of severe sepsis such as acute kidney injury ($p < 0.001$) (Table 2). Although the all-cause in-hospital mortality rate of 19% amongst those with no spleen was higher than that of 16% for those who had a spleen, this 3% absolute difference in mortality was not statistically significant ($p = 0.58$). Even in terms of those with the most severe IPD, 19 (51.4%) of the asplenic patients were admitted to the ICU and six (31.6%) died compared to 664 (27.7%) of the patients with a spleen of whom 192 (28.9%) died.

Table 1
Comparison of IPD patients with no spleen and IPD patients with a spleen

	No spleen	Spleen	*p*-Value
Number	37 (1.5%)	2398 (98.5%)	-
Age, years, mean (SD)	58.6 (13.7)	54.2 (17.9)	0.13
Male	18 (49%)	1362 (57%)	0.32
Aboriginal	0 (0%)	312 (13%)	0.011[a]
Living at home	36 (97%)	1924 (81%)	0.026[a]
Homeless	0 (0%)	184 (8%)	
Fully functional	28 (76%)	1727 (72%)	0.62
Current smoker	8 (22%)	1096 (46%)	0.003
Cancer past 5 years	12 (32%)	295 (12%)	<0.001
Hepatitis C	1 (3%)	306 (13%)	0.078
Chronic renal failure	3 (8%)	124 (5%)	0.44
HIV infection	0	117 (5%)	0.25[a]
Systemic lupus erythematosus	1 (3%)	16 (1%)	0.23
COPD	3 (8%)	438 (18%)	0.13
Alcoholism	4 (11%)	616 (26%)	0.039
Illicit drug use	1 (3%)	481 (20%)	0.006

IPD, invasive pneumococcal disease; SD, standard deviation; COPD, chronic obstructive pulmonary disease.
[a] Corrected for zero cell.

Table 2
Outcomes of IPD amongst patients with and without a spleen

	No spleen (37 cases)	Spleen (2398 cases)	*p*-Value
Intensive care admission	19 (51.4%)	664 (27.7%)	0.001
Mechanical ventilation	15 (40.5%)	532 (22.2%)	0.008
Meningitis	8 (21.6%)	112 (4.7%)	<0.001
Cellulitis	1 (2.7%)	64 (2.7%)	1
Osteomyelitis	0	7 (0.3%)	1
Septic arthritis	1 (2.7%)	39 (1.6%)	0.46
Acute kidney injury	7 (18.9%)	92 (3.8%)	<0.001
Liver failure	2 (5.4%)	60 (2.5%)	0.24
Died in hospital	7 (18.9%)	374 (15.6%)	0.58

IPD, invasive pneumococcal disease.

Table 3
The two most frequent pneumococcal serotypes causing IPD amongst 37 patients with no spleen and 2398 with a spleen

Serotype	No spleen	Spleen	*p*-Value
23B	10 (27.0%)	20 (0.8%)	<0.0001
22F	7 (18.9%)	169 (7.0%)	0.006
Total	17 (45.9%)	189 (7.8%)	

IPD, invasive pneumococcal disease.

3.3. Serotype data

Table 3 shows the two most common infecting pneumococcal serotypes according to the presence or absence of a spleen. Two serotypes, 23B and 22F combined, accounted for 45.9% of the infections in the asplenic group, but only 7.8% of the infections in the patients with a spleen. Serotype 23B with 10 isolates (27.0%) was 33 times more frequent in the asplenic group than in those with a spleen. The remaining serotypes in the asplenic group were 15C, 19A, 23A, 33A (two isolates of each) and 4, 9, 10A, 11A, 12F, 13, 15A, 20, 23F, 34, 35B (one isolate of each) and one non-type able serotype. Two of the serotypes causing infection in the asplenic patients, serotypes 4 and 23F, are in PCV7 (5.4%); these two plus two isolates of 19A are in PCV13 (10.8%) and an additional 11 isolates – 10A, 11A, 12F, 20 (one each), and 22F (seven) – are in PPV23 (40.5%). Twenty-one of the remaining serotypes (23B (10 isolates), 15C, 23A, 33A (two isolates each), and 9, 13, 15A, 23, 34, 35B (one isolate each)) are not in any of the currently available vaccines, and one isolate was non-type able.

4. Discussion

This study revealed several new findings that are important with respect to the management of patients with IPD in the absence of a spleen. Currently, the mortality rate for those with IPD and asplenia is not significantly different from that of patients who have a spleen. This study, extended over 15 years, included a total of 2435 patients with IPD of whom 37 (1.5%) lacked a spleen. This number of cases is larger than various previously published case series or single-center experiences, and a review of the existing literature indicates that this study provides comprehensive current data that fill an important gap in studies on the morbidity and mortality from IPD in asplenic patients from the late 1990s through to the present[2–4,8–11].

For instance, Rubin and Schaffner recently reviewed the care of the asplenic patient and found that amongst children with sickle cell disease and presumably functional asplenia and IPD, the mortality rate declined from 18% in the mid 1980s to 2–10% in studies of cases between 1994 and 2007. This article does not give current data on the mortality rate in asplenic adult patients with IPD, but indicates that between 1966 and 1996 it was 46%.[11]

In the current study, the pneumococcal infection in the asplenic group was more severe as judged by markers of supportive treatment intensity, which included ICU admission, mechanical ventilation, complications such as meningitis, and acute kidney injury; however, in both absolute and relative terms, the mortality rate was similar to that in those with a spleen. This still represents an improvement in comparison to earlier studies.[2,3] Whether this is due to general improvements in the care of very sick patients, partial protection afforded by pneumococcal vaccination, increased 'herd' immunity, or other factors is unclear. The asplenic group was not healthier than those with a spleen and had some of the risk factors for IPD-related mortality, as was found in a previous study.[12]

With the widespread application of pneumococcal vaccines there has been a change in serotype distribution causing IPD. In Germany, there has been an increase in serotypes 15A and 23B in the post pneumococcal conjugate vaccine era.[13] If this were the case in Alberta, one would not expect a differential increase in infecting serotypes in the splenectomy population unless other factors are operative. Rodrigo and Lim cited a study of adults with IPD in which older adults and individuals with a greater level of comorbid illness were affected by serotypes 3, 6A, 6B, 8, 19F, and 23 and this resulted in more severe illness and led to higher mortality in comparison with IPD due to serotypes 1 and 7F.[14]

In 2002, shortly after the onset of this study, PCV7 was incorporated into the childhood immunization program in Alberta, and in 2010 it was replaced by PCV13.[15] PPV23 has been used in Alberta since the late 1980s. There is now ample evidence of the effectiveness of PCV7 and PCV13. In the USA, PCV7 was 96% effective against vaccine serotypes in healthy children and 81% effective in those with co-existing diseases.[16] This beneficial effect has had a secondary beneficial effect in adults, where use of PCV13 in children has resulted in an overall decrease in IPD amongst adults of 12–32%, with a 58–72% decline for IPD due to PCV13 serotypes.[17] This beneficial effect is offset somewhat by the increase in IPD by non-pneumococcal conjugate vaccine serotypes, i.e., replacement serotypes.[18]

Patients who have had their spleen removed have been advised to be vaccinated against pneumococci since the availability of PPV23; more recently the recommendations have been updated to indicate that these individuals should receive both PPV23 and PCV13.[19,20] Fifty-nine percent of the infecting serotypes amongst the asplenic patients in the present study were not in any of the currently available vaccines. The paucity of vaccine serotypes causing infection may represent vaccine efficacy. The predominance of serotype 23B, which accounted for 27% of the isolates amongst the asplenic patients, is even more noteworthy when one considers that it was 33 times more common than in the patients with a spleen. The reasons for this remain to be determined.

A crude estimate of asplenic patients at risk and the IPD rate amongst these patients can be calculated using some 'back of the envelope' calculations and might be informative. There were 75 splenectomies in Northern Alberta per year yielding 825 patients over the duration of the study. It is reasonable to assume a 'steady state', since splenectomies have been performed for some time and it is estimated that the number of asplenic persons at risk of IPD each year is likely around 3000. With 2.46 cases of IPD amongst the splenectomy group per year in Northern Alberta, the rate of IPD is 82/100 000 adults. In the early conjugate vaccine era, the rate of IPD amongst adults >60 years (this group has the highest IPD rate amongst adults) in the USA was 49/100 000 per year.[17] Thus the rate of IPD amongst splenectomized patients is close to double (at least 1.67 times) the rate amongst adults with the highest rate in the early conjugate vaccine era. Clearly, splenectomy remains a major risk factor for IPD.

This study has several strengths: (1) the large sample size, (2) the wealth of clinical data, and (3) the availability of pneumococcal serotyping data, all of which are critical for providing an accurate

picture of IPD in asplenic patients. There are, however, several limitations. First, the study was not designed to determine why patients who have undergone a splenectomy get IPD or whether the IPD occurred early or late following splenectomy. Furthermore, it could not examine the issue of 'functional' asplenia, which may be more common than realized. Second, the indications for splenectomy in these patients are not known. Third, by design, it was not possible to capture pneumococcal disease not associated with bacteremia, nor could investigations of the infections due to other encapsulated organisms that patients with asplenia are prone to be performed. Fourth, there was no detailed information regarding vaccination status. As asplenic patients are routinely advised to receive pneumococcal vaccination, one may have expected to see a reduction in serotypes included in the vaccines with a possible shift to non-vaccine-related serotypes. Although an increase in 23B was seen – a serotype not included in the vaccines – asplenic patients also had a much higher rate of 22F, which is included in the current vaccine. Thus, how vaccinations could have affected the serology results is difficult to surmise. Fifth, this study may not have had sufficient power to find statistical differences in mortality between splenic and asplenic patients; however, even in absolute terms, the mortality rates were similar. Moreover, mortality information once the patient was discharged from hospital was not available, and nor was information regarding changes in functional status or post-discharge morbidities associated with illness.

It is concluded that asplenic patients constitute a minority of patients with IPD and whilst their infection is more severe, their all-cause in-hospital mortality rate is similar to that of patients with a spleen. A predominance of pneumococcal serotypes 23B and 22F in this population was noted. These findings suggest that the rate of IPD in this population is still too high and that targeted programs to reduce this rate are necessary. It is clear that pneumococcal vaccination recommendations in those who undergo splenectomy should be addressed carefully, and if these findings are replicated, existing vaccines should be reformulated to include additional serotypes in this population.

Author contributions

T.J.M. and G.J.T. designed the study, organized the data collection, and had full access to all of the data in the study. T.J.M., G.J.T., S.R.M, and D.T.E. wrote the manuscript. D.T.E. carried out the statistical analysis and also had full access to the data. All authors have seen and approved the final paper.

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