

Increased risk for invasive pneumococcal diseases in children with acute lymphoblastic leukaemia

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Received 5 February 2007; accepted for
publication 8 March 2007

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*ESPED is the German surveillance unit for rare
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from >99% of all German children's hospitals.
ESPED members, that have reported cases of
invasive pneumococcal diseases in children with
acute lymphoblastic leukaemia, are listed in the
'Appendix'.

Some 30 years ago, patients with anatomical or functional asplenia, in particular children with sickle cell disease, were identified to be at high risk for invasive pneumococcal disease (IPD) (Overturf *et al*, 1977). More recently, other conditions of immunodeficiency including human immunodeficiency virus (HIV) infection and previous haematopoietic stem cell transplantation have emerged as additional risk factors for IPD (Farley *et al*, 1994; Engelhard *et al*, 2002). However, very limited data, none of which is current, are available regarding the risk of IPD in children suffering from acute lymphoblastic leukaemia (ALL), the most common type of childhood malignancy. Based on leukaemia incidence data from the German childhood cancer registry and a nation-wide, active

Summary

Asplenia and other conditions of immunodeficiency are established risk factors for invasive pneumococcal disease (IPD). There are no current data available on the risk of IPD in children with acute lymphoblastic leukaemia (ALL), the most common type of childhood malignancy. This study combined data from a nation-wide surveillance for IPD and the German childhood cancer registry, and showed that children with ALL carry a more than 10-fold higher risk for IPD than the general paediatric population. As a substantial proportion of IPD occurs during maintenance chemotherapy, children with ALL may represent candidates for the evaluation of prophylactic interventions including vaccination.

Keywords: invasive pneumococcal disease, children, acute lymphoblastic leukaemia, epidemiology, prophylaxis.

hospital-based surveillance for IPD in children, we analysed the risk for IPD in children with ALL treated according to current therapy protocols of the Berlin-Frankfurt-Münster (BFM) group and the German co-operative study group for childhood acute lymphoblastic leukaemia (CoALL).

Methods

Study setting and design

Invasive pneumococcal disease cases were reported in an active hospital-based surveillance system in the German population aged under 16 years between January 1997 and June 2003.

During this study period, pneumococcal conjugate vaccination was not part of the routine primary immunisation programme in Germany. Patients were included in the study if they had been admitted to a paediatric hospital and *Streptococcus pneumoniae* was isolated from blood culture, cerebrospinal fluid, or a sample from any other normally sterile body site (von Kries *et al.*, 2000). Cases were collected on a monthly basis and were validated by subsequent questionnaires, which also asked for comorbidities thus enabling the identification of IPD cases in children with ALL.

Statistical analyses

The relative risk for IPD in children with ALL compared with the general paediatric population in Germany was estimated from the numbers observed and those expected, commonly referred to as standardised incidence ratio (SIR). Risk analysis was restricted to IPD cases occurring during the first 2 years following ALL diagnosis. The numbers expected for all considered age-groups (N_{exp}) was calculated using the formula

$$N_{\text{exp}} = 6.5 \sum_{i=0}^{14} I_{\text{IPD},i} \cdot n_i \cdot t_i$$

In this formula index i denotes the year of age, IPD, i the age-specific averaged annual IPD incidence in the general population, n_i the average population under risk with ALL in the respective age groups (derived from reports of the German childhood cancer registry from 1999 to 2003 at <http://www.kinderkrebsregister.de>), and t_i the years under risk following ALL diagnosis. The average annual age-specific incidence estimates for IPD ($I_{\text{IPD},i}$) in the general paediatric population were based on all hospital reports of IPD cases and the average population at risk in the respective age groups from January 1997 to June 2003 – these 6.5 years of observation are reflected in the factor 6.5. Confidence intervals for SIR estimates were calculated using an open access program from the Centre for Disease Control and Prevention [CDC; <http://www.sph.emory.edu/~cdckms/exact-midP-SMR.html> (Version: 4.11.19)] and P -values were calculated using Fisher's exact test. P -values <0.05 were considered significant.

Results and discussion

During the 6.5-year study period, 11 IPD cases were reported in a cohort of approximately 3200 children with ALL. Two of the IPD cases were observed in children suffering from ALL relapse (Table I). The median age at IPD onset was 6 (range: 2–12) years and 6/11 (55%) patients were male. 10/11 (91%) IPD cases presented as bacteraemic/septic infections, while one IPD case showed clinical signs of meningitis. Despite prompt initiation of intravenous antibiotic therapy in all cases, one patient died of pneumococcal sepsis. All other patients recovered without disabling sequelae. For 9/11 (82%) IPD cases, chemotherapy, ongoing at time of IPD onset, was

Table I. Clinical characteristics of reported IPD cases in children with ALL.

Year	Age, years	Sex	Chemotherapy	Type of IPD	Outcome
1997	9	m	Yes*	Bacteraemic pneumonia	Recovery
1998	4	f	Yes†	Bacteraemia	Recovery
1999	6	m	Yes†	Bacteraemia	Recovery
1999	6	m	No	Meningitis	Recovery
1999	2	m	Yes†	Bacteraemia	Recovery
2000	8	m	Yes*	Bacteraemia	Recovery
2000	12	f	Yes*	Bacteraemia	Recovery
2002	7	m	Yes*	Bacteraemia	Recovery
2002	2	f	Yes†	Bacteraemia	Recovery
2003	2	f	No	Bacteraemia	Recovery
2003	3	f	Yes*	Bacteraemia	Death

IPD cases observed in patients suffering from ALL relapse are printed in bold.

IPD, invasive pneumococcal disease; ALL, acute lymphoblastic leukaemia; m, male; f, female.

*Maintenance chemotherapy.

†Induction chemotherapy.

reported: maintenance therapy in five patients and induction therapy in four patients. In addition, two children presented with IPD at initial diagnosis of ALL before antineoplastic therapy was initiated (Table I). These clinical data imply that IPD should be considered a relevant differential diagnosis in children with ALL presenting with fever of unknown origin, not only during neutropenia following intensive chemotherapy but, more importantly, also during non-neutropenic treatment phases i.e. during maintenance therapy, when management of ALL patients presenting with fever without focus may not necessarily include prompt initiation of antibiotic therapy. Moreover, administration of trimethoprim/sulphamethoxazol, at least at dosages routinely given for *Pneumocystis jirovecii* prophylaxis during ALL therapy, does not provide protection from IPD.

Compared to the risk for IPD in the general population, the relative risk for IPD in children with ALL in the first 2 years after diagnosis was significantly increased by a factor of 11.4 [95% confidence interval (CI): 5.6–20.9]. The highest risk was observed in children from 5–9 years, who showed a 50.6-fold increase compared with the general population. Nevertheless,

Table II. Relative risk for IPD in children with ALL.

Age group, years	IPD cases expected	IPD cases observed	SIR	95% CI	P -value
0–4	0.651	5	7.6	(2.8–17.0)	<0.001
5–9	0.079	4	50.6	(16.1–122.1)	<0.001
0–14	0.787	9	11.4	(5.6–20.9)	<0.001

IPD, invasive pneumococcal disease; ALL, acute lymphoblastic leukaemia; SIR, standardised incidence ratio; CI, confidence interval.

even in the group of younger children from 0–4 years, the risk for IPD was significantly increased ($P = 0.001$; Table II). The absolute risk for IPD in paediatric ALL patients during the first two years after diagnosis was 2.8 (95% CI: 1.3–5.2) per 1000 cases of ALL and 1.4 (95% CI: 0.7–2.7) per 1000 person years when compared with a background rate of 0.040 (95% CI: 0.039–0.041) per 1000 persons years in the healthy pediatric population (von Kries *et al*, 2000). Regarding age groups, the absolute risk was highest for the 5- to 9-year-old group of children with ALL (2.4 IPD cases per 1000 person years and 4.2 IPD cases per 1000 ALL cases).

These estimates might have been biased by more complete reporting and case ascertainment in children with leukaemia. Reporting bias did not appear to be an issue: we compared the proportion of IPD cases reported by both the hospital-based Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland (ESPED) surveillance system and an independent database that collected IPD cases directly from microbiological laboratories, which were unaware of the cases' comorbidities. As these proportions were not significantly different between healthy children and ALL patients ($P > 0.1$), a relevant reporting bias seems unlikely. Ascertainment bias was possible, however: the probability of taking a blood culture in paediatric ALL patients with fever of unknown origin might be higher than in otherwise healthy children admitted to hospital for this condition. We therefore performed a sensitivity analysis, assuming an IPD case ascertainment rate of 50% in the general paediatric population as observed in a recent study on the blood culture sampling rate in children with pneumonia or fever of unknown origin (Rueggeberg *et al*, 2004). Even with these assumptions, the relative risk for IPD in children with ALL remains significantly increased by a factor of 5.7 (95% CI: 2.8–10.5; $P < 0.001$) underlining the validity of our findings.

To our knowledge, our data represent the first statistical estimate of IPD risk among children with ALL that includes an analysis of the relative IPD risk of paediatric ALL patients compared with the general paediatric population. We showed that the relative IPD risk in paediatric ALL patients was significantly increased, resulting in an absolute risk of one IPD episode per 357 cases of ALL. However, this absolute risk is likely to be an underestimate because, in our study, identification of IPD cases in ALL patients exclusively relied on hospital surveillance, which captures only about 40% of all IPD cases, as demonstrated by capture–recapture studies applying a second independent data source based on laboratory reports (von Kries *et al*, 2000). Therefore, the absolute risk for IPD in children with ALL is probably twofold higher, reaching approximately one IPD episode per 180 ALL cases or 5.6 IPD episodes per 1000 ALL cases. In this regard, our results compare well with data from the few prior studies analysing IPD in paediatric ALL patients in the early era of combination chemotherapy (Chilcote & Baehner, 1979; Siber, 1980; Allen & Weiner, 1981). Siber (1980) provided an absolute incidence rate of 13.3 IPD cases per 1000 patient years in children

with ALL treated between 1968 and 1977 in a large American paediatric cancer centre. Our report extended these observations to paediatric ALL patients treated according to current intensive therapy protocols and also showed that IPD episodes are equally likely to arise during neutropenia following intensive chemotherapy and non-neutropenic treatment phases i.e. during maintenance chemotherapy.

Preventive strategies for IPD including chemoprophylaxis and active immunization have proven efficacious in high-risk populations, such as children with sickle cell disease. The present study showed that the risk of IPD for children with ALL treated according to current therapy protocols was similar to the reported risk for children with sickle cell disease (12.3 IPD cases per 1000 person years) or for recipients of haematopoietic stem cell transplantation (8.1 IPD cases per 1000 transplantations), conditions for which preventive strategies have been implemented into routine practice (Pastor *et al*, 1998; Engelhard *et al*, 2002). As a significant proportion of IPD cases occur during maintenance chemotherapy, a treatment phase where efficient responses to vaccination have been documented (Ercan *et al*, 2005), pneumococcal immunisation of children with ALL might prevent IPD and therefore warrants evaluation in prospective trials.

Acknowledgements

The ALL incidence data were kindly provided by P. Kaatsch (German childhood cancer registry, Institute for Medical Biostatistics, Epidemiology and Informatics, University of Mainz, Germany). We thank U. Göbel (Clinic for Paediatric Oncology, Haematology and Clinical Immunology, University Clinic Düsseldorf, Germany) for critical review of the manuscript.

Potential conflict of interest

R.M., D.D., H.J.L. and R.v.K. have received research grants from Wyeth Pharma. All other authors: no conflicts.

Financial support

This analysis is a spin-off from a prospective study on active surveillance of invasive pneumococcal diseases in children in Germany, which was supported by an unrestricted research grant from Wyeth Pharma (to R.v.K.).

Appendix

Reporting members of the ESPED study group were as follows: U. Bierbach, D. Körholz (Universitätskinderklinik Leipzig), H. Schmid, K. Welte (Kinderklinik der Medizinischen Hochschule Hannover), U. Bode (Universitätskinderklinik Bonn), K. Ehlert, H. Christiansen (Universitätskinderklinik Marburg), E. Lutz, M. Sindichakis, P. Heidemann (I. Klinik für

Kinder und Jugendliche, Klinikum Augsburg), T. Lieber, H.I. Huppertz (Prof. Hess-Kinderklinik, Bremen), M. Rister (Klinikum Kemperhof, Koblenz), B. Wulff, W. Havers (Universitätskinderklinik Essen), T. Wygold, H. Jürgens (Universitätskinderklinik Münster).

References

- Allen, J.B. & Weiner, L.B. (1981) Pneumococcal sepsis in childhood leukaemia and lymphoma. *Pediatrics*, **67**, 292–295.
- Chilcote, R.R. & Baehner, R.L. (1979) Septicemia in association with acute lymphoblastic leukemia. *Journal of Pediatrics*, **94**, 715–718.
- Engelhard, D., Cordonnier, C., Shaw, P.J., Parkalli, T., Guenther, C., Martino, R., Dekker, A.W., Prentice, H.G., Gustavsson, A., Nurnberger, W. & Ljungman, P. (2002) Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. *British Journal of Haematology*, **117**, 444–450.
- Ercan, T.E., Soycan, L.Y., Apak, H., Celkan, T., Ozkan, A., Akdenizli, E., Kasapcopur, O. & Yildiz, I. (2005) Antibody titers and immune response to diphtheria-tetanus-pertussis and measles-mumps-rubella vaccination in children treated for acute lymphoblastic leukaemia. *Journal of Pediatric Hematology/Oncology*, **27**, 273–277.
- Farley, J.J., King, J.C., Nair, P., Hines, S.E., Tressler, R.L. & Vink, P.E. (1994) Invasive pneumococcal disease among infected and uninfected children of mothers with human immunodeficiency virus infection. *Journal of Pediatrics*, **124**, 853–858.
- von Kries, R., Siedler, A., Schmitt, H.J. & Reinert, R.R. (2000) Proportion of invasive pneumococcal infections in German children preventable by pneumococcal conjugate vaccines. *Clinical Infectious Diseases*, **31**, 482–487.
- Overturf, G.D., Powars, D. & Baraff, L.J. (1977) Bacterial meningitis and septicemia in sickle cell disease. *American Journal of Diseases of Children*, **131**, 784–787.
- Pastor, P., Medley, F. & Murphy, T.V. (1998) Invasive pneumococcal disease in Dallas County, Texas: results from population-based surveillance in 1995. *Clinical Infectious Diseases*, **26**, 590–595.
- Rueggeberg, J.U., Ketteler, K., MacKenzie, C.R., von Kries, R., Reinert, R.R. & Schroten, H. (2004) Blood culture sampling rates at a German pediatric university hospital and incidence of invasive pneumococcal disease. *Infection*, **32**, 78–81.
- Siber, G.R. (1980) Bacteremias due to *Haemophilus influenzae* and *Streptococcus pneumoniae*: their occurrence and course in children with cancer. *American Journal of Diseases of Children*, **134**, 668–672.