Published in final edited form as:

AIDS. 2011 March 13; 25(5): 717–720. doi:10.1097/QAD.0b013e3283440583.

Incidence of and Risk Factors for Community Acquired Pneumonia in US HIV-Infected Children, 2000–2005

Andrew P. Steenhoff, MD^{1,2}, Joshua Josephs³, Richard M. Rutstein, MD¹, Kelly A. Gebo, MD, MPH³, George K. Siberry, MD, MPH⁴, Aditya H. Gaur, MD⁵, Robert Warford, NP⁶, P. Todd Korthuis, MD, MPH⁷, Stephen A. Spector, MD⁸, and Samir S. Shah, MD, MSCE^{1,2}

¹Department of Pediatrics, Children's Hospital Philadelphia, Philadelphia, PA

²Division of Infectious Diseases, Children's Hospital Philadelphia, Philadelphia, PA

³Department of Medicine, Johns Hopkins University, Baltimore, MD

⁴Department of Pediatrics, Johns Hopkins University, Baltimore, MD

⁵Infectious Diseases, St Jude's Children's Research Hospital, Memphis, TN

⁶Pediatrics, St Luke's/Roosevelt Hospital Center, NY, NY

⁷Medicine, Oregon Health and Science University, Portland, OR

⁸Pediatric Infectious Diseases, University of California San Diego, San Diego, CA, United States

Summary

The incidence of and risk factors for community-acquired pneumonia (CAP) are described from 2000–2005 in a multicenter US cohort of HIV-infected children. In 736 patients, 87 episodes of CAP (33.2 events/1,000 PY) had a mean CD4% of 23% (controls: 30%) and mean CD4 count of 668 cells/mm³ (controls: 870 cells/mm³). CAP incidence decreased 44% from 2000–2001 to 2002–2005. On multivariate analysis, viral load > 100,000 copies/mL (OR 3.98; CI: 1.05–15.13) was associated with CAP. Herd immunity through pneumococcal immunization may have diluted the effect of individual immunization in this cohort.

Keywords

HIV; Pneumonia; Pediatric

Pneumonia burden is substantially higher in HIV-infected compared with HIV-uninfected children (1–4). Following the 1996 introduction of highly active antiretroviral therapy

Address for correspondence and reprints: Dr. Andrew Steenhoff, Division of Infectious Diseases, 12th Floor Abramson Research Building, Children's Hospital of Philadelphia, 34th and Civic Center Blvd, Philadelphia, PA 19104. Telephone: 215-590-2017, Facsimile: 215-590-2025, steenhoff@email.chop.edu.

Conflict of interest: None reported.

Financial disclosure: Sponsorship was provided by the Agency for Healthcare Research and Quality, Rockville, Maryland (Fred Hellinger, Ph.D., John Fleishman, Ph.D., Irene Fraser, Ph.D.); Health Resources and Services Administration, Rockville, Maryland (Robert Mills, Ph.D.). Dr Steenhoff received support from the National Institutes of Health (NIH) Kirschstein T32 training grant AI 055435 and both Dr Steenhoff and Dr Rutstein received support from the University of Pennsylvania Center for AIDS Research (IP30AI45008-01). Dr. Korthuis' time was supported by the National Institutes of Health, National Institute on Drug Abuse (K23 DA19809).

Dr. Shah received support from the National Institute of Allergy and Infectious Diseases (K01 AI73729) and the Robert Wood Johnson Foundation under its Physician Faculty Scholar Program. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

(HAART), the incidence of bacterial pneumonia in HIV-infected children in the United States declined several-fold (4). Since 2000, widespread heptavalent conjugate pneumococcal (PCV7) vaccination (PCV7) has decreased the incidence of invasive pneumococcal disease in the general pediatric population (5–12). However, the incidence of community-acquired pneumonia (CAP) in HIV-infected children following PCV7 licensure is unknown.

This retrospective cohort study between January 1, 2000 and December 31, 2005 used the US multicenter HIV Research Network (HIVRN). Eligible subjects were HIV-infected, ≥21 years of age, and followed longitudinally. CAP was defined as clinician-diagnosed pneumonia in a patient initially evaluated in a primary care setting. Cases of *Pneumocystis jirovecii* pneumonia (PCP) were excluded. Change in CAP annual incidence was evaluated using χ^2 test for trend. Patients were matched on age category and year to account for known CAP risk factors (12) and to control for temporal factors such as changes in CAP incidence or influenza seasonal severity. Risk factor analysis using a 3:1 match for controls:cases explored associations between patient characteristics and CAP using bivariate and multivariate logistic regression, clustering by site of care. Variables with $P < 0.2$ were included in the multivariate model and the most parsimonious multivariate model was identified. Pneumococcal vaccination data from two sites were available for a sub-analysis. Vaccination status was defined as: “any vaccine,” ≥1 dose of either PCV7 or 23-valent pneumococcal polysaccharide vaccine (PS23); “vaccinated with PCV7,” ≥2 doses of PCV7; and “vaccinated with PS23,” ≥1 dose of PS23 in the 5 years preceding a CAP episode. Institutional review board approval was obtained at all sites.

From 2000 to 2005, 736 children were enrolled in the HIVRN and followed for 2,675 person years (PY). Characteristics at enrollment are summarized (Table). There were 87 CAP episodes; an incidence of 33.2 cases/1,000 PY. Peak incidence was 53.4 cases/1,000 PY in 2001 and nadir was 16.8 cases/1,000 PY in 2005. CAP incidence decreased by 44% when comparing 2000–2001 with 2002–2005 ($P < 0.01$). CAP incidence was higher in children <5 years of age (45.0/1,000 PY) than in children ≥5 years of age (30.9/1,000 PY). The nadir incidence occurred in 2004 for the ≥5 group (15.0; 95% CI 6.8–35.1) and in 2005 for the <5 group (19.2; 95% CI 0.5–103.0). When stratifying by mode of acquisition, the overall incidence was 37.2/1,000 PY in perinatally-infected children and 19.1/1,000 PY in the non-perinatal group. CAP occurred in 22 (39%) of 57 children prescribed PCP prophylaxis and in 4 (31%) of 13 children not prescribed prophylaxis.

In matched comparison of cases and controls, the mean CD4 percentage was 23% and 30%, and the median CD4 count was 668 cells/mm³ and 870 cells/mm³ respectively. In unadjusted bivariate analysis, a viral load ≥100,000 copies/ml and a CD4 percentage <15% (Table) were risk factors. In multivariate analysis, a viral load ≥100,000 copies/ml remained a risk factor.

Vaccination data prior to an episode of CAP were available for 102 (89%) of 114 patients; 14% of the cohort. Ninety-two (90%) of 102 had received any pneumococcal vaccine; 23 (23%) ≥2 PCV7 doses; and 79 (77%) PS23. Of cases, 32 of 34 (94%) received any pneumococcal vaccine compared with 60 of 68 (88%) controls ($P = 0.35$). For PCV7, 15 of 34 (44%) cases and 16 of 68 (24%) controls were recipients ($P = 0.03$). In bivariate sub-analysis limited to subjects with vaccination data, pneumococcal vaccination rates did not differ between cases and controls for any definition of appropriate vaccination.

A temporal decrease in incidence of CAP occurred from 2000 to 2005 in HIV-infected children and adolescents in the USA. The degree to which this decline was attributable to conjugate pneumococcal vaccine or HAART-derived immune benefits is unknown.

However, analysis of a subset of the cohort did not support a protective effect of pneumococcal vaccination.

The finding that the incidence of CAP in HIV-infected children has decreased is important. A crucial next step is to ascertain whether the incidence of CAP in this group is approaching that in the general pediatric population. If not, the reasons for this, such as suboptimal vaccination response, will need to be established to inform future intervention strategies.

Our findings on univariate analysis that a viral load $\geq 100,000$ copies/ml and CD4 percentage below 15% are associated with CAP is consistent with previous reports (4, 13). These highlight the importance of ensuring sustained, rather than just initial, viral load control and CD4 percentage response following HAART. On multivariate analysis, only viral load $\geq 100,000$ copies/mL was associated with CAP.

The lack of association between inadequate vaccination and CAP is surprising. Widespread PCV7 immunization in the US has resulted in herd immunity (13) which may have diluted the effect of vaccination in this study. In addition, this suggests that HAART-derived immune reconstitution may be a more important protective factor against CAP, though this finding requires confirmation in larger studies.

In our study, CAP incidence was similar in those prescribed PCP prophylaxis compared to those not. Studies examining the effects of trimethoprim-sulfamethoxazole on the risk of bacterial infections have demonstrated varied results (14, 15). We speculate that although PCP prophylaxis likely provides some level of protection against CAP of bacterial etiology, it has no effect against CAP of viral etiology.

Study limitations included the unknown vaccine status of the whole cohort, no data on MAC prophylaxis and the potential that CAP diagnosis could be subject to misclassification. Such misclassification is however unlikely because clinicians used a consistent definition of CAP. In addition, any misclassification should not differ between 2000–2001 and 2002–2005.

A temporal decrease in incidence of CAP occurred from 2000 to 2005 in HIV-infected children and adolescents. Ongoing monitoring of CAP in HIV-infected children must remain an important priority until their risk is no greater than that seen in their HIV-uninfected peers. Herd immunity through pneumococcal immunization may have diluted the effect of individual immunization in this cohort.

References

1. Mofenson LM, Yogev R, Korelitz J, et al. Characteristics of acute pneumonia in human immunodeficiency virus-infected children and association with long term mortality risk. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. *The Pediatric infectious disease journal*. 1998; 17:872–880. [PubMed: 9802627]
2. Madhi SA, Petersen K, Madhi A, Wasas A, Klugman KP. Impact of human immunodeficiency virus type 1 on the disease spectrum of *Streptococcus pneumoniae* in South African children. *The Pediatric infectious disease journal*. 2000; 19:1141–1147. [PubMed: 11144373]
3. Jones N, Huebner R, Khoosal M, Crewe-Brown H, Klugman K. The impact of HIV on *Streptococcus pneumoniae* bacteraemia in a South African population. *AIDS (London, England)*. 1998; 12:2177–2184.
4. Gona P, Van Dyke RB, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. *Jama*. 2006; 296:292–300. [PubMed: 16849662]
5. Black SB, Shinefield HR, Ling S, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. *The Pediatric infectious disease journal*. 2002; 21:810–815. [PubMed: 12352800]

6. Byington CL, Samore MH, Stoddard GJ, et al. Temporal trends of invasive disease due to *Streptococcus pneumoniae* among children in the intermountain west: emergence of nonvaccine serogroups. *Clin Infect Dis*. 2005; 41:21–29. [PubMed: 15937758]
7. Kaplan SL, Mason EO Jr, Wald ER, et al. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. *Pediatrics*. 2004; 113:443–449. [PubMed: 14993532]
8. Black S, Shinefield H, Baxter R, et al. Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in Northern California Kaiser Permanente. *The Pediatric infectious disease journal*. 2004; 23:485–489. [PubMed: 15194827]
9. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *The New England journal of medicine*. 2003; 348:1737–1746. [PubMed: 12724479]
10. Schutze GE, Tucker NC, Mason EO Jr. Impact of the conjugate pneumococcal vaccine in arkansas. *The Pediatric infectious disease journal*. 2004; 23:1125–1129. [PubMed: 15626950]
11. Haddy RI, Perry K, Chacko CE, et al. Comparison of incidence of invasive *Streptococcus pneumoniae* disease among children before and after introduction of conjugated pneumococcal vaccine. *The Pediatric infectious disease journal*. 2005; 24:320–323. [PubMed: 15818291]
12. Grijalva CG, Nuorti JP, Arbogast PG, et al. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. *Lancet*. 2007; 369:1179–1186. [PubMed: 17416262]
13. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease--United States, 1998–2003. *Mmwr*. 2005; 54:893–897. [PubMed: 16163262]
14. Hughes WT, Dankner WM, Yogev R, et al. Comparison of atovaquone and azithromycin with trimethoprim-sulfamethoxazole for the prevention of serious bacterial infections in children with HIV infection. *Clin Infect Dis*. 2005; 40:136–145. [PubMed: 15614703]
15. Buskin SE, Newcomer LM, Koutsky LA, et al. Effect of trimethoprim-sulfamethoxazole as *Pneumocystis carinii* pneumonia prophylaxis on bacterial illness, *Pneumocystis carinii* pneumonia, and death in persons with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1999; 20:201–206. [PubMed: 10048909]

Table 1

Characteristics of 736 children at time of enrollment into the HIV Research Network (HIV RN) and univariate and multivariate risk factors for pneumonia.

Variable	Number Overall (%)	Among Cases and Controls	Controls	Cases	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P-value
Age *							
0 to <5	174 (24)	89 (24)	65 (24)	24 (26)	*	*	*
5 to <10	174 (24)	100 (27)	75 (28)	25 (27)		...	
10 to 21	388 (52)	175 (48)	132 (49)	43 (47)		...	
Male sex	345 (47)	163 (45)	118 (43)	45 (49)	1.22 (0.74–2.02)	...	
Race							
White	85 (12)	47 (13)	36 (13)	11 (12)	0.54 (0.22–1.33)	...	
Black	519 (70)	253 (69)	192 (71)	61 (66)	Reference	...	
Hispanic	117 (16)	59 (16)	39 (14)	20 (22)	1.17 (0.51–2.65)	...	
Other	15 (2)	5 (2)	5 (2)	0			
Private Insurance	60 (8)	32 (9)	29 (11)	3 (3)	0.55 (0.20–1.48)	...	
HAART	514 (70)	288 (79)	212 (78)	76 (83)	1.14 (0.58–2.26)	...	
No PCP Prophylaxis Prescribed	464 (63)	225 (62)	175 (64)	50 (54)	1.41 (0.34–7.03)	...	
No MAC Prophylaxis Prescribed	687 (93)	319 (88)	255 (93)	64 (70)	1.5 (0.02–39.23)	...	
CD4 ⁺ T Lymphocytes, %							
>25	341 (46)	180 (58)	138 (60)	42 (53)	1.0 (Reference)	1.0 (Reference)	...
15 to 25	153 (21)	80 (26)	60 (26)	20 (25)	1.51 (0.80–2.85)	1.84 (0.89–3.80)	0.09
<15	92 (13)	50 (16)	32 (14)	18 (23)	2.98 (1.19–7.41)	1.98 (0.63–6.23)	0.24
Missing±	150 (20)	54 (15)	42 (15)	12 (13)	...	...	...
HIV Viral Load, copies/ml							
<400	119 (16)	97 (29)	76 (30)	21 (26)	1.0 (Reference)	1.0 (Reference)	...
400 to 9,999	234 (32)	130 (39)	106 (42)	24 (30)	1.41 (0.68–2.91)	1.48 (0.59–3.72)	0.51
10,000 to 99,999	124 (17)	59 (18)	43 (17)	16 (20)	2.39 (1.03–5.55)	1.46 (0.48–4.48)	0.41
100,000	111 (15)	46 (14)	26 (10)	20 (25)	5.21 (2.02–13.47)	3.98 (1.05–15.13)	0.04
Missing±	148 (20)	32 (8.88)	21 (8)	11 (12)			
HIV Risk Factor							

Variable	Number Overall (%)	Among Cases and Controls	Controls	Cases	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P- value
Perinatal infection	489 (66)	200 (74)	76 (83)	76 (83)	0.93(0.43–2.00)		

Notes:

* Analysis was matched on age therefore this variable was not adjusted for; ±Patients with missing data were excluded from the analysis.