1425. Population Pharmacokinetic Analysis of Ciprofloxacin and Levofloxacin in Critically Ill Trauma, Surgical, and Burn Patients
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Session: 145. PK/PD Studies
Friday, October 5, 2018: 12:30 PM

Background. Antibiotic pharmacokinetics (PK) differ between critically ill and noncritically ill patients, as do the bacteria causing infection, yet dosing regimens are derived from noncritically ill populations. The purpose of this study was to examine the adequacy of ciprofloxacin and levofloxacin dosing in critically ill trauma, surgery, and burn patients for treating common nosocomial pathogens.

Methods. Time–concentration curves derived from plasma samples in critically ill patients receiving ciprofloxacin 400 mg IV q12h (N = 11) or q24h (N = 5) or levofloxacin 750 mg IV q24h (N = 9) were used to calculate individual PK parameters and create population PK models. Monte-Carlo simulations were performed to assess the cumulative fraction of response (CFR) to achieve the target pharmacodynamic index (PDI) of AUC:MIC ≥ 125, using Gram-negative MIC distributions from the European Committee on Antimicrobial Susceptibility Testing.

Results. The fit of both the ciprofloxacin and levofloxacin population models was improved with the addition of GgC as a covariate. Despite simulating higher dosing regimens, such as ciprofloxacin 600 mg q8h and 800 mg q8h and levofloxacin 1,125 mg q24h and 1,500 mg q24h, only a single dosing regimen (Gram-negative species combination) demonstrated a CFR ≥ 90%. This result was consistent with the finding that the maximum MICs at which individual patients achieved the target PDI were well below the CLSI breakpoints of ciprofloxacin and levofloxacin for Enterobacteriaceae, Pseudomonas, and Acinetobacter isolates with MICs up to the CLSI breakpoints. When increased doses were simulated, the CFR of all but one dose/species combination remained suboptimal. Individualized dosing guided by therapeutic drug monitoring may be an appropriate next step to improve fluoroquinolone efficacy in these critically ill patients.

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1426. Impact of Routine Pediatric PCV13 on the Incidence and Severity of Invasive Pneumococcal Disease in Adults in Ontario, Canada
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Background. Monitoring the incidence and severity of disease due to varied pneumococcal (Pn) serotypes (STs) over time is important in assessing the benefit of Pn vaccines. We describe changes in adult IPD after the 2010 introduction of routine infant PCV13 in Ontario, Canada (PCV13 is funded only for immunocompromised adults ≥50 years as of 2015).

Results. Of 6,275 episodes of adult IPD, 5,674 (90%) have STs and 6,007 (98%) detailed clinical data. Incidence of IPD decreased from 14.2/100,000/year in 1995 to 6.0/100,000/year in 2013–2017. One thousand two hundred and three (19%) adults with IPD were 15–44 years, 1,889 (30%) were 45–64 years, 3,182 (51%) were 65 years.

Figures 1 and 2 show rates over time by ST group and age. In multivariable analyses, there was no difference across vaccine ST groups (nonvaccine type (NVT) vs. PPV23 not PCV13 vs. PCV13) in patient age, proportion with ICU admission, requirement for mechanical ventilation (MV), death, length of stay (LOS) or diagnosis of meningitis, except that patients with NVT isolates were more likely to require ICU admission (OR 1.5, 95% CI 1.2–2.0), and to have meningitis (OR 1.9, 95% CI 1.1–3.3). Case fatality declined from 25% (480/1,949) 1995–2001 to 19% (148/763) in 2012–2017 (multivariable OR/year 0.98 95% CI 0.97–0.99); requirements for ICU admission (26–31%); OR/year 1.02, 95% CI 1.01,1.03) and MV (OR/year 18–22%; 1.02, 95% CI 1.01–1.03) increased, LOS did not change. From 2013 to 2017, the distribution of vaccine group STs has not changed: 37% PCV13 (383/1,031); 20% PCV20not13 (205); 9% PPV23not20 (94), 34% NVT (349). NVT strains include over 23 ST, most commonly 23A (72, 21%), 15A (46, 13%), 35B (37,11%), 6C (36, 10%), 23B (20, 8%).

Conclusion. In our population, with infant but no routine adult PCV13, the incidence of adult IPD appears to have stabilized, with PCV13 ST strains contributing 37% of IPD. Case fatality has decreased; ICU admission increased. Adult vaccination may be required to further reduce PCV13 ST infections.

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broader serotype coverage. The aim of this study was to estimate the population-level impact of new PCVs by replacing the existing 13-valent vaccine (PCV13) in infants.

**Methods.** An age-structured dynamic transmission model of Streptococcus pneumoniae before and after PCVs introduction was developed. The model was fit to longitudinal Active Bacterial Core surveillance (ABCs) data (1997–2015) in the United States on distribution and cases of IPD, as well as population level prevalence and serotype distribution data. It was assumed that total S. pneumoniae carriage remains constant over time, with full carriage replacement within four years of introduction of any PCV. Two alternative new PCVs with differing IPD coverage are tested with an introduction date of 2020.

**Results.** When compared with continuing vaccination of infants with PCV13, 10 years after a new PCV is introduced (2,034) cases of IPD are substantially reduced (shown in the table below). Broader serotype coverage leads to greater reductions in IPD. The greatest IPD reduction occurred in infant vaccine-based PCV subtypes, but even similar reductions are also observed in the unvaccinated elderly population due to herd protection.

| Additional Vaccine Coverage Over PCV13 (2012/2024) | <2 Years | 2–5 Years | 50–64 Years | >65 Years | All Ages |
|---|---|---|---|---|---|
| 11–21% | 22–35% | 36 35 33 31 31 |
| 15–30% | 42 42 41 39 40 |

*Defined as the proportion of IPD cases that are caused by serotypes covered by the new PCV in 2016/2018 (a range of values is given because of differences by age group; values differ between 2016 and 2024 as serotype prevalence has not reached steady state as of 2016).

**Conclusion.** A new, higher valent PCV given to infants in the United States has the potential to reduce future cases of IPD. Vaccination of infants may also have a substantial indirect benefit on IPD cases in adults and the elderly.

**Disclosures.** N. Madin-Warburton, Sanofi Pasteur: Consultant, IQVIA received consulting fee. A. B. Pitcher, Sanofi Pasteur: Consultant, IQVIA received consulting fee. M. H. Kyaw, Sanofi Pasteur: Employee, Salary. A. Kieffer, Sanofi Pasteur: Employee, Salary.

1428. Modeling Reductions in Antibiotic Prescriptions due to Otitis Media in Canada as a Result of Pneumococcal Conjugate Vaccination

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**Background.** Vaccines are an important factor in combating the growing global health issue of antimicrobial resistance. Pneumococcal conjugate vaccines (PCVs) have substantially reduced the burden of otitis media (OM) caused by S. pneumoniae, one of the largest causes of antibiotic prescriptions (Abx) in children under 5. The purpose of this study was to quantify the number of Abx received since the introduction of a national PCV program in Canada.

**Methods.** We adapted a previously published forecasting model to estimate the reduction in OM cases in Canada since the introduction of PCVs in all routine PCV periods. Over 10 years, PCVs were estimated to avert 3.7 million cases of OM in children and 1.5 million cases of OM in adults in Canada. This corresponded to an estimated reduction of 3.3 million Abx, or 0.96 Abx per PCV dose per year. Over 10 years, PCVs were estimated to avert 3.7 million cases of OM in Canada.

**Results.** Over 10 years, PCVs were estimated to avert 3.7 million cases of OM in Canada. The model was fit to longitudinal Active Bacterial Core surveillance (ABCs) data (1997–2015) in the United States on distribution and cases of IPD, as well as population level prevalence and serotype distribution data. It was assumed that total S. pneumoniae carriage remains constant over time, with full carriage replacement within four years of introduction of any PCV. Two alternative new PCVs with differing IPD coverage are tested with an introduction date of 2020.

**Results.** When compared with continuing vaccination of infants with PCV13, 10 years after a new PCV is introduced (2,034) cases of IPD are substantially reduced (shown in the table below). Broader serotype coverage leads to greater reductions in IPD. The greatest IPD reduction occurred in infant vaccine-based PCV subtypes, but even similar reductions are also observed in the unvaccinated elderly population due to herd protection.

| Additional Vaccine Coverage Over PCV13 (2012/2024) | <2 Years | 2–5 Years | 50–64 Years | >65 Years | All Ages |
|---|---|---|---|---|---|
| 11–21% | 22–35% | 36 35 33 31 31 |
| 15–30% | 42 42 41 39 40 |

*Defined as the proportion of IPD cases that are caused by serotypes covered by the new PCV in 2016/2018 (a range of values is given because of differences by age group; values differ between 2016 and 2024 as serotype prevalence has not reached steady state as of 2016).

**Conclusion.** A new, higher valent PCV given to infants in the United States has the potential to reduce future cases of IPD. Vaccination of infants may also have a substantial indirect benefit on IPD cases in adults and the elderly.

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1430. Evolving Impact of 13-Valent Pneumococcal Conjugate Vaccine on Invasive Pneumococcal Disease

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**Session:** 146. Pneumococcal Vaccines  
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**Background.** The 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 in the childhood immunization schedule in Massachusetts (MA) beginning in April 2010. We describe the current epidemiology of invasive pneumococcal disease (IPD) in Massachusetts (MA) children after introduction of PCV13.

**Methods.** Cases of invasive pneumococcal disease (IPD) in children <18 years of age were identified through the enhanced surveillance system in MA since 2001. All cases in children and Streptococcus pneumoniae (SP) isolates, when available, are submitted to Department of Public Health (MDPH) and parents/physicians are interviewed for confirmation of demographic and clinical data. All available isolates are confirmed by sp, serotyped by Quellung reaction.

**Results.** There were 351 IPD cases in MA children from April 1, 2010 to September 31, 2017, and 36 (10.3%) were in infants <6 months; 42 (12.0%) in children between 6 and 12 months; 63 (18.0%) in toddlers 12–24 months; 102 (29.1%) in children 2–5 years, and 108 (30.8%) were in children aged 5–19 years. Incidence of IPD declined to 6.8/10,000 (95% CI 2.6–11.1) in 2015/2016 period which represents a 72.1% decline compared with 2010/2011 (24.4/10,000, 95% CI 16.3–32.5) (figure). However, in 2016/2017, IPD incidence increased to 10.4/10,000 (95% CI 5.2–15.7). The most common clinical presentation was bacteremia (62.9%), followed by pneumonia (30.5%) and CNS disease (6.6%). Among, 103 (32.6%) children had at least 1 comorbidity, asthma (13.2%), hematologic malignancy (12.1%), prematurity (9.9%) and sickle cell disease (9.9%) were the most common comorbidities. He overall mortality rate was 5.1%. Isolates from 308 (89.3%) were available for serotyping; vaccine serotypes (VST) were identified in 372 (91.2%), 7F (46.2%), 19F (19.9%), 3 (17.9%), 19F (10.4%), 6A (2.8%), 14, 18C, 5 (9.0%) each. Serotypes 15B (13.7%), 22F (12.6%) and 33F (11.8%) were the most common nonvaccine serotypes (NVT).

**Conclusion.** Invasive pneumococcal disease identified in the post-PCV13 era is primarily caused by NVTs, specifically serotypes 15B, 33F and 22F; and disproportionately observed in children with comorbid conditions. Continued surveillance is necessary to determine the impact of PCV13, as well as track potential changes in disease incidence and character due to NVT.