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Advances in Pediatric Pharmacology, Therapeutics, and Toxicology

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Abstract

Significant advancements have been made in pediatric therapeutics and pharmacology over the last two years. In the United States, passage of the Food and Drug Administration Safety and Innovation Act has made the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act permanent, and ensured that studies will be conducted in neonates. In Europe, the Pediatric Regulation, which went into effect in early 2007, has also provided a framework encouraging an expansion of pediatric research. Because of such regulatory involvement, a greater number of studies are being performed, and more pediatric dosing, efficacy, and safety information is being incorporated into product labels. The goal of this publication is to highlight important advancements made in the field of pediatric pharmacology, toxicology, and therapeutics from January 2012 to December 2013.

Keywords

pediatrics; pharmacology; pharmacokinetics; toxicology

INTRODUCTION

Significant advancements have been made in pediatric therapeutics over the last two years. Of note, the U.S. Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law on July 9, 2012, making the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) permanent for the Food and Drug Administration (FDA), no longer requiring reauthorization every five years. BPCA, which was also authorized for the National Institutes of Health (NIH) for the next five years, provides a mechanism for off-patent drug development and a pediatric exclusivity incentive,

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encouraging manufacturers to perform pediatric studies in exchange for an additional six months of patent protection. PREA gives the FDA the authority to require that studies be performed if the indication being sought for approval in adults is relevant to child health. As a result of BPCA and PREA, pediatric labeling information has improved, but one analysis reported that, as of 2009, only 46% of drugs had some labeling information related to pediatric use, an increase from the 22% estimated in 1975; also 41% of new molecular entities had pediatric labeling, up from 20% in 1999 [1]. A summary of select labeling changes made by the FDA in 2012 and 2013 is presented in Table 1.

In Europe, the Pediatric Regulation went into effect in 2007 to promote the expansion of pediatric research in this region. The European Medicines Agency (EMA) highlighted successes over the first five years of the regulation and reported that about 400 clinical trials including children (0–18 years) are performed each year. The EMA Pediatric Committee has agreed to over 600 Pediatric Investigational Plans (PIPs) with pharmaceutical companies, and a large collaboration of pediatric research networks (Enpr-EMA) has been created [2]. More pediatric research has translated into more information in the Summary of Product Characteristics: 221 changes with regards to safety and efficacy, 89 additions of dosing information, and 77 other modifications related to new study data being added [2].

An important requirement in FDASIA and in the EMA Pediatric Regulation is that clinical trials also be performed in neonates when appropriate because neonates historically have been excluded from drug trials far too often. If neonatal studies are not warranted or cannot be performed for logistical or ethical reasons, sponsors must provide justification. This provision is important as limited pharmacokinetic (PK) and pharmacodynamic (PD) data are available in this vulnerable population. Between 1997 and 2012, only 31 drug products were studied in neonates, resulting in labeling changes for 27; these figures are relatively small when compared with pediatric studies performed in older age groups for more than 400 drug products [3]. A separate analysis indicated that approximately 54% of neonatal labeling changes resulted in addition of the following statement: “safety and efficacy have not been established”[4]. For the remaining 46% (4 HIV drugs, 3 anesthesia drugs, 4 drugs for other indications), an approval for use in neonates was obtained [4]. Therefore, there is an overall lack of PK/PD data in neonates, in particular premature infants, and clinical trials are not being performed for widely prescribed medications in this population.

Another concern receiving considerable attention relates to drug shortages. Drug shortages can be problematic because they cause clinicians to alter drug treatment and, in some cases, prescribe less effective or more toxic medications. For example, for the treatment of Hodgkin’s lymphoma in children, one study reported less favorable outcomes when cyclophosphamide was prescribed in place of mechlorethamine as a result of a drug shortage [5]. One survey found that 83% of oncologists polled reported being unable to prescribe standard chemotherapy due to drug shortages [6]. In February 2012, the American Academy of Pediatrics (AAP) submitted testimony to the U.S. House of Representatives Committee on Energy and Commerce Subcommittee on Health stressing the impact of drug shortages for pediatricians [7]. Then, in March 2013, AAP provided comments on the establishment of an FDA Drug Shortages Task Force and Strategic Plan [8]. Pursuant to FDASIA, the FDA was asked to develop this task force to address drug shortages; as stated in the FDA’s

strategic plan, the task force's goal will be to develop mitigation strategies when the agency is informed of a drug shortage and a long-term prevention plan [9].

In light of the aforementioned developments, the goal of the present work is to highlight important advancements made in the fields of pediatric pharmacology, toxicology, and therapeutics from January 2012 to December 2013. Select articles were chosen to identify important developments within various therapeutic areas with the exception of oncology, where only FDA label changes made over the last two years are highlighted.

ANESTHESIA

Pharmacokinetics

Etomidate is a hypnotic drug used for induction of general anesthesia. Due to a lack of data, it is not currently recommended for use in children <10 years of age [10]. With the goal of describing the drug's disposition in children, a population PK analysis was performed [11]. Forty-nine children with a median age of 4 years (range 0.53–13.21 years) undergoing elective surgery received an intravenous bolus dose of etomidate (0.3 mg/kg). After accounting for size-based differences (i.e., body weight) in PK parameters, an increased clearance and central volume of distribution was observed for younger children (0.5 vs. 4 years reported). Hemodynamic changes were stable, and only slight decreases in systolic blood pressure were noted. As a result, the authors suggest that younger children may require higher bolus doses [11].

Sedation

Dexmedetomidine, an intravenous α_2 -adrenergic agonist, is widely prescribed off-label as a sedative agent for children. Dexmedetomidine is currently not approved by the U.S. FDA or EMA for use in pediatric patients as efficacy and safety have not been established, but the lack of respiratory depression and relatively short half-life (~2 hours) are major advantages to the use of this agent. Unfortunately, few studies have evaluated the use of dexmedetomidine in children. A retrospective analysis evaluated the safety and efficacy of prolonged dexmedetomidine use in critically ill children with cardiovascular disease [12]. A total of 52 children (median age 10.5 months; interquartile range 5.8–20 months) received dexmedetomidine via continuous infusion for at least 96 hours. When compared with control patients who received conventional sedative agents (e.g., midazolam), no differences were noted in mechanical ventilation, intensive care unit length of stay, heart rate, or blood pressure measurements between treatment groups. Moreover, dexmedetomidine use was associated with a shorter duration of continuous midazolam and morphine infusions. No serious safety concerns were reported. In a small sample of heart failure patients, dexmedetomidine did not appear to effect heart rate, mean arterial pressure, or inotrope score when the drug infusion was stopped [13].

Another retrospective analysis evaluated outcomes of hypotension, hypertension, and bradycardia in a large sample (n=669) of children (median age 4.5 years; range 0.1–22.5 years) who received dexmedetomidine for sedation during nuclear medicine imaging [14]. Hypotension, hypertension, and bradycardia, defined as a 20% or greater deviation from age-adjusted awake normal values, occurred in 58.7%, 2.1%, and 4.3% of children,

respectively. Older children (age categories 3–6 and 6–12 years) experienced a significantly greater number of hypotensive and bradycardic events relative to younger peers. None of these events, however, required pharmacological treatment.

In a prospective, randomized, double-blind, clinical trial, intranasal dexmedetomidine was compared with intranasal midazolam in 90 children (median age 6 years; interquartile range 2–9) undergoing adenotonsillectomy [15]. All patients also received general anesthesia with nitrous oxide, oxygen, and sevoflurane administered via a face mask. Midazolam and dexmedetomidine were found to be equally effective with regards to decreasing anxiety following separation from parents, but midazolam was superior in obtaining satisfactory mask induction (82.2% vs. 60%, $P=0.01$).

CARDIOLOGY

Pulmonary Hypertension

Sildenafil is a phosphodiesterase-5 inhibitor used for the treatment of pulmonary arterial hypertension (PAH). In adults, sildenafil is labeled for the treatment of PAH, whereas it is used off-label in children. The Sildenafil in Treatment-Naïve Children With Pulmonary Arterial Hypertension trial (STARTS-1) was a randomized, double-blind, placebo-controlled, dose-ranging study designed to evaluate the safety and efficacy of sildenafil citrate administered to children (age 1–17 years weighing ≥ 8 kg) with PAH [16]. With regards to efficacy, percent change in peak oxygen consumption reached only marginal significance for all dose groups combined, although improvements, including hemodynamics and functional class, were noted for the medium and high groups when compared with placebo. For safety outcomes, sildenafil was well tolerated over a 16-week period; however, in the STARTS-2 trial, long-term treatment (>2 years) with high doses resulted in greater mortality [16]. On August 30, 2012, the FDA issued a Drug Safety Communication informing clinicians of the STARTS-2 findings and reminding them that use in children is an off-label recommendation, not approved by the agency [17]. Also, the EMA revised its Summary of Product Characteristics to inform clinicians that doses higher than those recommended by the agency should not be used in pediatric patients with PAH [18].

Hypertension

In obese children and adolescents, identifying and treating systemic pre-hypertension (systolic or diastolic blood pressure $\geq 90^{\text{th}}$ and $<95^{\text{th}}$ percentile) is important, as this group of patients is at risk for progression to hypertension [19,20]. Some have hypothesized that uric acid may play an important role in hypertension and cardiovascular disease. A randomized, double-blind trial was performed to assess the impact of uric acid reduction in obese adolescents treated with allopurinol, probenecid, or placebo [20]. Patients treated with urate-lowering drugs had a significant reduction in systolic (-10.2 vs. 1.7 mm Hg), diastolic (-9 vs. 1.6 mm Hg), and systemic vascular resistance when compared with placebo. These results indicate that in pre-hypertensive, obese adolescents, uric acid reduction may play a role in reducing blood pressure.

Few studies of anti-hypertensive agents in children have been conducted over the past two years. The PK and safety of the antihypertensive agent olmesartan medoxomil was evaluated in children and adolescents (12 months – 16 years) [21]. Olmesartan is an angiotensin II receptor blocker used in the treatment of hypertension. Although one of the goals of this study was to collect data in children 12–23 months of age, no patients in this age group were enrolled. In the older age groups, a total of 24 hypertensive patients were studied. Body size-adjusted oral clearance (CL/F) and volume of distribution (V/F) estimates were found to be similar to those in adults (CL/F 0.06–0.1 L/h/kg; V/F 0.32–0.49 L/kg). No serious adverse effects were reported. Another study evaluated the safety PK of the phosphodiesterase III inhibitor, milrinone, which is used off-label in the pediatric population for the treatment of pulmonary hypertension [22]. Eleven neonates with persistent pulmonary hypertension received milrinone as an intravenous loading dose (50 µg/kg) over 60 minutes and a maintenance infusion (0.33–0.99 µg/kg/min) for 24–72 hours. When compared with a published study in older children (mean [range] 4.7 [0.7–15]) [23], both clearance (0.11 vs. 0.6 L/kg/h) and steady-state volume of distribution (0.6 vs. 1.5 L/kg) were lower in neonates. In patients with a poor response to inhaled nitric oxide, improvements in pulmonary and systemic hemodynamics were noted.

Congenital Heart Disease

Systemic-to-pulmonary artery shunts are placed in some patients with cyanotic congenital heart disease. Due to the risk for shunt thrombosis, antiplatelet agents are frequently prescribed. A multicenter, double-blind, event-driven trial randomized infants to clopidogrel 0.2 mg/kg/day (n=467) or placebo (n=439) to assess whether addition of clopidogrel to conventional therapy improved shunt-related morbidity or all-cause mortality [24]. No differences were noted between the groups for the primary composite end point or in any subgroup analyses or in bleeding rates. The results of this trial indicate that clopidogrel did not provide any additional benefit over conventional therapy alone.

DERMATOLOGY

The American Acne and Rosacea Society published guidelines, which were reviewed and endorsed by the AAP, that specifically address the management of pediatric acne [25]. The expert recommendations provide a framework for: classification of pediatric acne on the basis of age and form of presentation; severity assessment; and treatment algorithms. Potential treatment options discussed include: over-the-counter (OTC) use of topical benzyol peroxide, topical retinoids, topical/oral antibiotics, isotretinoin, and hormonal therapy. Additional considerations such as medication adherence, selection of an appropriate formulation, impact of previous treatment and history, prevention of bacterial resistance, and psychological factors are also discussed.

GASTROENTEROLOGY

Crohn's Disease

Crohn's disease is a chronic, systemic inflammatory condition that can affect any part of the gastrointestinal tract. Crohn's disease cases in children can be of greater severity than those in adults, and approximately 18% of patients require surgery within five years of disease

onset [26]. Initial treatment of the disease in children includes corticosteroids or enteral nutrition, with the latter favored in Europe, followed by use of immunomodulatory drugs (e.g., azathioprine, 6-mercaptopurine) [27,28]. Thalidomide is an immunomodulatory drug that may be effective as an alternative treatment in some Crohn's disease patients [29]. A multicenter, randomized, double-blind, placebo-controlled clinical trial evaluated use of thalidomide on clinical remission in 56 children (mean age ~15 years, range 2–18 years) with active Crohn's disease despite being on immunosuppressive treatment [26]. Clinical activity was assessed at predefined time points using a validated clinical activity index, the Pediatric Chronic Disease Activity Index (PCDAI) score. The primary study outcome was clinical remission at week 8, defined as a PCDAI score of 10 or less and a reduction in the PCDAI score of at least 25% or 75% at weeks 4 and 8, respectively. Patients were administered thalidomide (1.5–2.5 mg/kg/day) or placebo for 8 weeks. In an open-label extension study, patients originally randomized to placebo and who were not in remission or did not have at least a 75% reduction in their PCDAI score were given thalidomide for an additional 8 weeks. Responders to treatment were followed for at least 52 weeks. Out of 28 and 26 children administered thalidomide and placebo, respectively, greater clinical remission was observed with drug treatment (13/28 [46.4%] vs. 3/26 [11.5%]); risk ratio 4.0 [95% confidence interval {CI} 1.2–12.5]; $P=0.01$). In the open-label phase, for patients initially randomized to placebo and then administered thalidomide, 11 of 21 (52.4%) had reached clinical remission at week 8 (risk ratio 4.5 [95% CI 1.4–14.1]; $P=0.01$). The most common serious adverse effect was peripheral neuropathy, with an incidence of 1 per 1000 patient-weeks for clinical manifestations (no electromyography alterations) to 2.7 per 1000 patient weeks for electromyography alterations (no clinical manifestation). The results of this study showed that thalidomide resulted in greater clinical remission at 8 weeks and long-term maintenance of remission when compared with placebo [26].

Tumor necrosis factor (TNF) antagonists are also effective in the treatment of Crohn's disease. Infliximab is approved by the FDA and EMA for treatment of moderate-to-severe Crohn's disease in pediatric patients 6 years of age or older who fail to respond to conventional treatments (corticosteroids, enteral nutrition, and immunomodulators). In a phase 3, multicenter, randomized, open-label trial, the TNF antagonist adalimumab was studied in children with severe Crohn's disease [30]. The percentage of patients in clinical remission at weeks 26 and 52 were 33.5% and 28.4%, respectively. No statistically significant differences were noted between high- and low-dose groups (38.7% vs. 28.4%, $P=0.075$). The safety profile was found to be comparable to that observed in adults.

Interestingly, in a separate analysis, data collected from a large prospective, observational study (RISK: Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease) was used to assess whether early (within 3 months of diagnosis) treatment with TNF antagonists improves one-year outcomes when compared with early immunomodulator monotherapy [28]. Immunomodulatory therapy included azathioprine, 6-mercaptopurine, and methotrexate. A propensity score analysis was performed to compare study outcomes between treatment groups. The authors reported that early treatment with an anti-TNF α drug was associated with greater remission than early treatment with an immunomodulator (85.3% vs. 60.3%; relative risk 1.41 [95% CI 1.14–1.75]; $P=0.0017$). With regards to early immunomodulator

therapy versus no early immunotherapy, no differences were noted in achieving remission at one year (60.3% vs. 54.4%; relative risk 1.11 [95% CI, 0.83–1.48]; $P=0.49$). The authors acknowledge that additional data are needed to identify which children would be most likely to benefit from treatment with anti-TNF α agents [28].

Constipation

When patients with autism spectrum disorder suffer from gastrointestinal discomfort, such as diarrhea, constipation, and dyspepsia, identification, diagnosis, and treatment of these symptoms is challenging. The Gastroenterology Committee of the Autism Speaks Autism Treatment Network (ATN) performed a systematic review of the literature and field testing with the goal of generating a treatment algorithm useful for clinicians [31]. Using the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) treatment guideline for constipation as an initial template, an optimized guideline for children with autism was developed—first, by expert opinion and then by applying the optimized algorithm in four pilot sites where the feasibility was evaluated by autism health care providers. Atypical and in particular self-abusive behavior and posturing (e.g., grimacing, holding abdomen), were noted as potential signs and symptoms of constipation. Field testing demonstrated that the algorithm was “readily applied and did not interrupt the clinic flow,” as well as highlighted the importance of follow-up visits and identifying nonresponders early in treatment [31]. Treatment options and appropriate dosages were also noted. The authors observed that children with autism may not respond as favorably to standard treatment due to “volume, texture, or taste sensitivities” [31].

Dyspepsia

Cyproheptadine, a serotonin and histamine antagonist, has been used in children as an appetite stimulant. One study sought to evaluate the use of cyproheptadine in children and adolescents with dyspeptic symptoms who were refractory to other treatment options (dietary changes, H₂-antagonists and/or proton pump inhibitors) [32]. A retrospective open-label study was performed with response to cyproheptadine treatment assessed at clinic visits. Patients with both idiopathic disease, as well as those with a known pathophysiological cause for the dyspepsia (e.g., fundoplication), were included in the analysis. Out of 80 total patients, 44 responded to treatment ($n=33$ had a “significant response”; symptoms resolved in 11). In a multivariate analysis, a superior response was noted in children <12 years of age and in females. Also, the frequency of responders was higher ($12/14=86\%$) in patients who received the drug following Nissen fundoplication. The most common side effects were somnolence (16%), irritability and behavioral changes (6%), weight gain (5%), and abdominal pain (2.5%).

INFECTIOUS DISEASES

Pharmacokinetics

Over the last two years, advancements have been made in characterizing drug disposition for several anti-infective agents (Table 2). Characterizing the PK of drugs in children is critical to account for physiologic and developmental changes that may affect drug exposure.

Pneumonia

Clinical practice guidelines (CPG) can provide a framework for clinicians to diagnose and treat medical conditions and can potentially affect antimicrobial selection, costs, and outcomes. One study sought to evaluate the impact of institutional CPG for community-acquired pneumonia (CAP) on hospital length of stay, readmission within 14 days of discharge, and antibiotic selection, among other outcomes [50]. A multicenter retrospective cohort study was performed using data collected through the Pediatric Health Information Database. Data from 43 tertiary care children's hospitals were reviewed; a survey sent to each institution to query the availability of a CPG; and relevant outcomes compared between institutions with and without CPGs. Out of 43 hospitals, 41 completed the survey (95%), and 13 (32%) indicated that they had an institutional CPG for non-severe CAP. Significant between-institution variability in the recommendations for diagnostic testing was noted by the investigators. For the 19,710 children included in the analysis, no differences were noted between institutions with and without CPGs for the following outcomes: hospital length of stay, hospital readmissions at 14 days, hospital costs, or ordering patterns for most diagnostic tests. The exception to the latter was institutions that recommended viral testing (e.g., influenza or respiratory syncytial viral testing) were more successful in having this test performed. In contrast, antibiotic drug selection was associated with CPG recommendations. At institutions with a CPG, penicillins and aminopenicillins were more likely to be prescribed when recommended as first-line treatment (46.3% vs. 23.9%). As a result, the authors concluded that the availability of CPGs did not affect resource utilization, whereas antibiotic impact was notably different.

In a separate study, the impact of CPGs on antibiotic management of children with CAP was investigated [51]. A retrospective analysis was performed using medical records of patients discharged from Children's Mercy Hospital in Kansas City, Missouri, 12 months before and after the CPG was introduced. Moreover, the impact of an antimicrobial stewardship program was also assessed. A total of 1,033 patients were included in the analysis: 530 (51%) before and 503 (49%) after introduction of the CPG. The key recommendations in the CPG were use of empirical treatment with ampicillin, then use of amoxicillin upon discharge, and a treatment duration of 5–7 days [51]. The authors reported that use of the CPG successfully led to an increased use of ampicillin (13% before vs. 63% after) and a decrease in ceftriaxone prescribing (72% before vs. 21% after). For discharge antibiotics, there was also a statistically significant increased use of amoxicillin ($P<0.001$), while prescribing of cefdinir and amoxicillin-clavulanate was significantly lower ($P<0.001$); the combined effect of the CPG and antimicrobial stewardship program resulted in decreases of 12% and 16%, respectively. In uncomplicated CAP, the use of a CPG and antimicrobial stewardship program successfully aided in changing antimicrobial prescribing patterns at one institution.

For the treatment of severe pneumonia, a randomized, double-blind, placebo-controlled clinical trial was performed to assess the benefit of zinc supplementation as adjuvant therapy in 610 children [52]. The primary outcome, time to cessation of severe pneumonia (defined using the Integrated Management of Childhood Illness algorithm), was assessed in a total of 580 children (2–35 months age) who were enrolled in the study until recovery from the

condition (288 zinc; 292 placebo). A standardized treatment algorithm was used for all patients, and zinc or placebo was administered as a single oral dose for up to 14 days. Neither the median time to cessation of severe pneumonia nor the risk of treatment failure was significantly different between the zinc and placebo groups, although marginal differences were noted. The results of the study do not provide compelling evidence to recommend use of zinc as adjuvant therapy in young children with severe pneumonia.

Intra-abdominal Infections

Meropenem is a broad-spectrum antibiotic currently approved by the FDA for the treatment of bacterial meningitis and/or complicated intra-abdominal infections in children 3 months of age. The results of an open-label, 24-center, prospective, multi-dose, PK, safety, and effectiveness study in infants <91 days of age treated with meropenem for suspected or confirmed intra-abdominal infection were recently published [53]. Dosing groups evaluated were based on gestational age (GA) and postnatal age (PNA): group 1 (GA <32 weeks, PNA <2 weeks), 20 mg/kg every 12 hours; groups 2 (GA <32 weeks, PNA 2 weeks) and 3 (GA 32 weeks, PNA <2 weeks), 20 mg/kg every 8 hours; and group 4 (GA 32 weeks, PNA 2 weeks), 30 mg/kg every 8 hours. Treatment duration lasted between at least 3 and up to 21 days. A total of 200 infants were enrolled in the study, 142 (71%) of whom were <32 weeks GA. In terms of efficacy, out 192 infants, therapeutic success was reported in 162 (84%). The lowest frequency of success (29/39 [74%]) was observed for infants in group 1 (GA <32 weeks, PNA <2 week). Adverse events were reported for 99 infants (50%), of which 30 in 21 infants were deemed to be possibly related to meropenem. Moreover, there were 36 serious adverse events in 34 infants (17%), of which two were deemed possibly related to meropenem. The most common adverse effects were sepsis (6%), seizures (5%), elevated conjugated bilirubin (5%), and hypokalemia (5%). The study results demonstrate that most infants met the criteria for therapeutic success, and meropenem was generally well tolerated.

Hepatitis B

Adefovir dipivoxil and tenofovir disoproxil fumarate are both nucleotide analogs with activity against the hepatitis B virus. Moreover, both are FDA-approved for treatment against hepatitis infection in patients 12 years of age or older. Two separate studies were performed to study the safety and efficacy of these agents in the pediatric population. First, the results of a long-term (up to 240 weeks), open-label study evaluating adefovir use in 162 pediatric patients originally enrolled in a 48-week, double-blind, placebo-controlled trial were reported [54]. Following the original 48-week study, continued viral suppression and normalization of alanine aminotransferase was observed for patients on adefovir alone or in combination with lamivudine. Virologic failure was reported for 61/162 patients on adefovir; hepatitis B envelope antigen (HBeAg) and surface antigen seroconversion were reported in 55 and 5 subjects, respectively. Adefovir resistance was reported for one treatment-naïve child who was on monotherapy. Adefovir was generally well tolerated during long-term use.

A separate double-blind, placebo-controlled study evaluated the efficacy and safety of tenofovir disoproxil fumarate in adolescents (12 to <18 years of age) [55]. A total of 101 patients completed 72 weeks of tenofovir treatment, with the primary outcome being

virologic response (<400 copies/mL hepatitis B DNA) at week 72. Patients were randomized to once-daily tenofovir disoproxil fumarate 300 mg (n=52) or placebo (n=54). In the tenofovir treatment group, 89% (46/52) of patients had a virologic response, compared with 0% (0/54) in the placebo group. No resistance development to tenofovir was observed. Tenofovir was well tolerated by patients, and only one serious adverse effect was reported (hepatitis) in this group.

HIV

HIV-infected children can suffer from neurodevelopmental delay or encephalopathy. To evaluate the impact of early versus delayed treatment with antiretroviral therapy (ART) in HIV-infected children, the Children with HIV Early Antiretroviral Therapy (CHER) trial prospectively enrolled and compared neurodevelopmental outcomes in 90 infants of median age 11 months (age range 10–16 months; 64 infants on early ART; 26 on deferred treatment) [56]. For infants in the delayed treatment group, ART was deferred until clinical or immunological progression was observed. In the early treatment arm, ART was limited to 40 or 90 weeks. A neurological examination and the Griffiths Mental Development Scales (GMDS) were performed at the study visit closest to 10–12 months of age and used to assess neurodevelopmental outcomes. The median time to start ART in the early versus delayed treatment groups was 8.4 vs. 31.4 weeks, respectively. Using the GMDS, all scores were found to be lower in the deferred treatment group, and the general and locomotor scores, in particular, were significantly lower, indicative of superior neurodevelopmental outcomes with early treatment. Moreover, scores in the early treatment group were found to be similar to HIV-uninfected infants (except on the locomotor subscale) who were HIV-exposed or -unexposed.

The CHER trial also compared immunological, clinical, and virological outcomes between early time-limited ART (restricted to 40 or 96 weeks) and deferred treatment [57]. A total of 377 infants were enrolled (median age 7.4 weeks; interquartile range ~6.4–9 weeks). The primary outcome was time to failure of first-line ART (zidovudine, lamivudine, and lopinavir/ritonavir) or death. Infants were randomized to one of three treatment strategies: deferred therapy, early ART restricted to 40 weeks, and early ART restricted to 96 weeks. Treatment failure was defined as a CD4-positive T lymphocytes (%) decrease to less than 20% from week 24, CDC severe stage B or C events, or regimen-limiting toxicity. An HIV-RNA viral load of 10,000 copies per mm³ was considered virological failure. Relative to subjects in the deferred treatment arm, the hazard ratios for early therapy restricted to 40 and 96 weeks were 0.59 (95% CI 0.38–0.93, P=0.02) and 0.47 (0.27–0.76, P=0.002), respectively [57].

A separate randomized trial performed in six African countries and India sought to compare nevirapine versus ritonavir-boosted lopinavir plus zidovudine and lamivudine in 288 children 2–36 months of age with no prior exposure to nevirapine [58]. Due to its low cost, stability at high temperatures, acceptable safety profile, and the availability of fixed-dose combination, nevirapine is frequently an important treatment option for children in resource-limited settings [58]. For children younger than 2 years of age, the World Health Organization guidelines for ART currently recommend ritonavir-boosted lopinavir for

children with previous nevirapine (maternal or infant) exposure, and nevirapine in the absence of previous antiretroviral exposure [59]. The primary end point in the trial was treatment failure, defined as virologic failure or discontinuation of nevirapine or ritonavir-boosted lopinavir component of the ART at 24 weeks. The percentage of children with treatment failure was significantly greater in the nevirapine group when compared with ritonavir-boosted lopinavir (40.8 versus 19.3%, $P<0.001$). In addition, the time to a protocol-defined toxicity end point was significantly shorter for the nevirapine group. It is possible that resistance to nevirapine played a role in the poorer efficacy outcomes. Nineteen out of 32 patients in the nevirapine group with resistance data available were reported resistant at the time of treatment failure. The authors concluded that, in children with no prior exposure to nevirapine, more favorable outcomes were observed with patients treated with ritonavir-boosted lopinavir.

Influenza

Trivalent influenza vaccines contain two influenza A strains and one B strain. For influenza B, an important contributor of disease in children, there are two genetically distinct lineages of the hemagglutinin gene, which encodes a glycoprotein important for viral binding to cells [60]. Between 2001 and 2011, the correct B lineage was only selected five out of 10 times, suggesting there is a need for a quadrivalent vaccine that includes both [61]. A phase 3, randomized, double-blind study evaluated the immunogenicity and safety of a quadrivalent split virion influenza vaccine (QIV) versus a trivalent vaccine (TIV) in children 3–17 years of age [62]. A total of 2,738 children received QIV or TIV-B/Victoria or TIV-B/Yamagata in a 1:1:1 fashion. In addition, an additional 277 children age 6–35 months were enrolled in an open-label group administered QIV. Blood samples were collected on day 0 (prior to vaccination) as well as 28 days after the last vaccine dose, and then antibody titers were assessed using a hemagglutination-inhibition assay. The authors reported that QIV showed superior immunogenicity versus TIV with regards to the additional B strain and thus may offer improved protection against influenza B in children [62]. Safety of QIV was similar to that of TIV. Favorable immunogenicity was also shown against all four strains in the open-label group.

A separate randomized, multicenter study compared two trivalent live attenuated vaccines (T/LAIV), each containing a strain for each influenza B lineage, versus a quadrivalent live attenuated vaccine (Q/LAIV) [63]. A total of 2,312 patients in two age groups (2–8 years, 9–17 years) were randomized to one of the three groups. The Q/LAIV was found to be non-inferior to T/LAIV in terms of immunogenicity for children 2–17 years of age. As in the previous study, safety was also comparable between treatment groups.

NEUROLOGY

Migraines

Triptans are an important treatment option for migraine prevention in adults. Until recently, only almotriptan was indicated for use in adolescents (12–17 years), and none are approved for treatment in younger age groups. In late 2011, the FDA approved rizatriptan for use as migraine treatment in children as young as 6 years of age [64]. Since its approval, the results

of PK, safety, and efficacy studies performed in the pediatric population have been published.

First, to evaluate the PK and tolerability of rizatriptan, a randomized, double-blind, placebo-controlled, parallel group, single-dose study was performed in patients 6–17 years of age with a history of migraines [65]. Rizatriptan oral disintegrating tablets (ODT) were administered using a weight-based dosing scheme: children <40 kg received rizatriptan ODT 5 mg or placebo; 40 kg received 10 mg ODT or placebo. When area under the concentration versus time curve from zero to infinity ($AUC_{0-\infty}$) and maximal drug concentration (C_{max}) were compared with adult historical data (rizatriptan ODT 10 mg), the ratios in the <40 kg group were 0.85 (90% CI 0.73–0.98) and 1.07 (90% CI 0.86–1.34), respectively. For the 40 kg group, $AUC_{0-\infty}$ and C_{max} ratios were 1.17 (90% CI 1.02–1.34) and 1.06 (90% CI 0.87–1.30), respectively. Second, in terms of efficacy, rizatriptan was superior to placebo in patients 12–17 years of age and for the primary outcome, pain resolution at 2 hours (30.6% vs. 22%, $P=0.025$) [66]. In the 6–11 years age category, greater response (2-hour pain freedom) was observed with rizatriptan, but it did not reach statistical significance ($P=0.269$). These results may be related to a small sample size in this age category, as the study was powered for the adolescent (12–17 years) and combined 6–17 years age groups [66]. When the two age groups were combined (6–17 years), rizatriptan was significantly superior to placebo in terms of 2-hour pain freedom (33% vs. 24.2%, $P=0.01$). The proven efficacy in the 6–17-year-old age group, with comparable efficacy between the two subgroups (6–11 years vs. 12–17 years), and favorable safety profile served as the basis for regulatory approval [67].

Clinical trials evaluating migraine response to treatment in children are challenging because of a high placebo response rate that may result from inadequate study design and short duration of migraine attacks, among other factors [68]. A systematic analysis of trial data submitted to the FDA for approval as acute treatment of migraine attacks in the pediatric population was assessed to identify causes of study failures [69]. Clinical trial data for sumatriptan succinate, zolmitriptan, eletriptan hydrobromide, almotriptan malate, and rizatriptan benzoate were included in the analysis. A high placebo response rate was reported across trials: 53–57.5% for pain relief at 2 hours [69]. The authors emphasized the benefit of using a double randomization strategy whereby patients with an early placebo response are not included in a second randomization phase. This strategy was used for rizatriptan and resulted in a 6% reduction in the placebo response rate compared with a previous trial [69].

A separate meta-analysis evaluated evidence of effectiveness for prophylactic treatment of migraines in the pediatric population (<18 years) [70]. Data for 21 clinical trials were included: 13 placebo-controlled and 10 active-comparator trials (two comparator trials included placebo, too). Drugs found to be more effective than placebo were topiramate (difference in headaches per month, -0.71 ; 95% CI -1.19 to -0.24) and trazodone (-0.6 ; 95% CI -1.09 to -0.11), whereas clonidine, flunarizine, pizotifen, propranolol, and valproate were ineffective [70]. A significant placebo response was reported: a reduction in headaches from 5.5 (95% CI 4.52–6.77) to 2.9 (95% CI 1.66–4.08) per month. The authors

noted that there are only limited data available evaluating use of pharmacologic for prevention of migraine headaches in children [70].

Seizures

Topiramate (Topamax®) is an antiepileptic drug approved for use as monotherapy or adjunctive therapy in children 2 years of age treated for partial onset or primary generalized tonic-clonic seizures. A phase 1, safety and PK study sought to evaluate topiramate use in infants (n=55, 1–24 months of age) with refractory partial-onset seizures [71]. A total of four dose groups were evaluated: 3, 5, 15, or 25 mg/kg/day, with infants stratified into a dose group based on age category (1–6, 7–12, and 13–24 months). The oral liquid or sprinkle capsule formations were administered. In subjects with complete PK profiles (n=35), linear PK and dose proportionality were observed across all dose groups [71]. Drug clearance values on a per-kilogram basis were higher in infants (1–24 months) relative to published values in children and adolescents [71]. Patients receiving enzyme-inducing anti-epileptic drugs had two-fold higher clearance values. The most commonly reported adverse effects were upper respiratory tract infection (15%), fever (15%), vomiting (13%), somnolence (11%), and anorexia (11%).

A recent study sought to characterize the PK of lorazepam following single-dose administration to pediatric patients (5 months – 17 years) in status epilepticus (n=48) or patients with a history of seizures recruited as part of an elective cohort (n=15) [72]. The population estimates for clearance, half-life, and volume of distribution were 1.2 mL/min/kg, 16.8 hours, and 1.5 L/kg, respectively. Lorazepam clearance values normalized by body weight reported in this study were approximately 20% higher than those in adults. The authors report that a 0.1 mg/kg dose would be expected to achieve lorazepam concentrations of ~100 ng/mL and stay in the range of 30–50 ng/mL for 6 to 12 hours, where the latter concentration is expected to provide anticonvulsant effects while minimizing the drug's sedative effects. In terms of efficacy, of the 48 patients with status epilepticus, 42 were successfully treated with one or two doses, whereas six required three doses.

In a double-blind, randomized, non-inferiority trial, intravenous lorazepam was compared with intramuscularly administered midazolam for the treatment of status epilepticus in both pediatric and adult patients [73]. Subjects who experienced convulsions for greater than five minutes and were still convulsing at the time paramedics arrived on scene were administered a study medication. The primary outcome—absence of seizures before arriving to the emergency department and in the absence of rescue therapy—was compared between treatment groups. In the intramuscular midazolam group, 329 of 448 (73.4%) of patients were no longer convulsing upon arrival to the emergency department, compared with 282 of 445 (63.4%) in the intravenous lorazepam group. As a result, the authors reported that intramuscular midazolam was at least as effective intravenous lorazepam when administered by paramedics before arrival to the hospital [73].

ONCOLOGY

Four label changes were made for oncology drugs between 2012 and 2013 [64]. First, for palifermin (Kepivance), based on a phase 1 study in 27 pediatric patients, use is now indicated in children ages 1–16 years with acute leukemia undergoing hematopoietic stem cell transplant. Second, for patients ≥ 1 year of age and with tuberous sclerosis complex, everolimus (Afinitor Disperz®) is now approved for treatment of subependymal giant cellastrocytoma (SEGA). For bendamustine hydrochloride (Treanda®) and temsirolimus (Torisel®), label changes include a statement informing clinicians that effectiveness has not been established in pediatric patients.

PULMONARY AND ALLERGY

Asthma

It is hypothesized that asymptomatic gastroesophageal reflux can be a contributor of poor asthma control in children. In The Study of Acid Reflux in Children with Asthma, investigators compared the impact of lansoprazole, a proton pump inhibitor, on asthma control in 306 pediatric patients (6 and 17 years) [74]. A randomized, double-masked, placebo-controlled, parallel study in children with poor asthma control and no symptoms of gastroesophageal reflux disease (GERD) showed no statistically significant differences in the Asthma Control Questionnaire (ACQ) and in secondary outcomes including forced expiratory volume after one second (FEV1) and quality of life after 24 weeks of treatment. In addition, in a subgroup analysis (n=115) where esophageal pH study results were available, 49 patients were found to have positive results indicative of gastroesophageal reflux. When compared with patients with normal esophageal pH, lansoprazole did not appear to affect any study outcomes. With regards to toxicity, a greater number of upper respiratory tract infections, sore throats, and episodes of bronchitis were reported in patients receiving lansoprazole. These study results demonstrate that, in patients with poorly controlled asthma and no symptoms of gastroesophageal reflux, addition of lansoprazole did not improve treatment outcomes.

In a genetic substudy, 279 of the 306 aforementioned participants provided DNA for analysis [75]. The frequency of adverse events with lansoprazole was evaluated in children with single-nucleotide polymorphisms (SNPs) in *CYP2C19* as this gene may affect lansoprazole clearance and exposure. Patients were classified as poor metabolizers if they carried at least one *CYP2C19**2, *3, *8, or *9 allele, whereas extensive metabolizers were those patients with two wild type alleles. The frequency of upper respiratory tract infections was highest in poor metabolizers when compared with extensive metabolizers (69% vs. 60%), and both groups had higher frequencies than that observed with placebo (48%, $P=0.0039$, Cochran-Armitage test for trend). Likewise, the frequency of sore throat was higher in poor metabolizers (66%) when compared with extensive metabolizers (45%) or placebo (38%, $P=0.0015$, Cochran-Armitage test for trend). Blood samples were collected in some patients (2–3 hours after final dose) for lansoprazole concentration measurement. Mean plasma concentrations were significantly higher in poor versus (n=23, 207 ± 179 ng/mL) extensive (n=33, 132 ± 141 ng/mL) metabolizers ($P=0.04$). If these findings are replicated in an independent sample, the results may be clinically meaningful as a dosage

adjustment may be performed to mitigate the occurrence of these side effects in patients classified as poor metabolizers [75].

Inhaled glucocorticoids are the mainstay of therapy for most children with asthma. When inhaled glucocorticoids are administered to prepubertal children, a reduction in growth velocity can occur. However, the relationship between chronic use of inhaled glucocorticoids and attainment of adult height is not well understood [76]. The Childhood Asthma Management Program (CAMP) was a clinical trial that enrolled 1,041 children 5–13 years of age and compared the safety and efficacy of budesonide, nedocromil, and placebo [77]. Children in this study were followed long-term, and adult height was assessed at a mean (standard deviation) age of 24.9 (2.7) years [76]. Budesonide, an inhaled glucocorticoid, resulted in a 1.2 cm lower adult height (95% CI –1.9 to –0.5) when compared with placebo ($P=0.001$). In contrast, patients administered nedocromil, a mast cell stabilizer, had a 0.2 cm lower adult height (95% CI –0.9 to 0.5), although not statistically significant. The reduction observed in the budesonide group was similar to that reported after two years of treatment (–1.3 cm; 95% CI –1.7 to –0.9). Moreover, in the first two years of treatment, a larger daily budesonide dose was associated with a lower adult height (–0.1 cm for each microgram per kg body of body weight). The authors concluded that, although the reduction in growth velocity observed in the first two years of treatment persisted into adulthood, the benefits of these drugs in persistent asthma is well established. The use of the lowest effective dose is encouraged to minimize the impact on growth velocity.

For asthma, a notable drug label change was reported by the FDA for montelukast (Singulair®), which is now indicated for the treatment of exercise-induced bronchoconstriction in children as young as 6 years of age (previously 15 years or older) [64].

Allergic Rhinitis

Drug label changes or approvals were made for three drugs indicated to treat allergic rhinitis: the combination product azelastine hydrochloride and fluticasone propionate; azelastine; and beclomethasone dipropionate. The combination product azelastine hydrochloride 0.1%/fluticasone propionate 0.037%, which is administered as a nasal spray, was approved for the treatment of allergic rhinitis in children >12 years of age who require both an H_1 -antagonist and corticosteroid for symptomatic relief. The age category for which azelastine is indicated for treatment of seasonal and perennial allergic rhinitis was expanded to included 6–12 years (previously >12 years). Beclomethasone dipropionate, an intranasal corticosteroid, is now indicated for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in children >12 years of age. QNasl is formulated as a non-aqueous-based formulation and thus may be less susceptible adverse reactions that result from post-nasal drip [78].

Cystic Fibrosis

A significant advancement was made in the treatment of cystic fibrosis with the approval of the new chemical entity ivacaftor. Ivacaftor is approved for the treatment of cystic fibrosis in patients ≥6 years and with the *G551D* mutation in the cystic fibrosis transmembrane

conductance regulator (*CFTR*) gene. This new drug potentiates the action of the CFTR protein, a chloride-ion channel, by affecting the “channel-open probability” and facilitating ion transport [79].

SYMPTOMATIC CARE

Analgesia

To investigate the opioid-sparing effects of intravenous acetaminophen in neonates and infants undergoing major noncardiac surgery, a randomized, double-blind, single-center study was performed [80]. A total of 71 neonates or infants (age <1 year) were enrolled and followed for 48 hours following major thoracic or abdominal surgery. Patients were randomized to receive morphine (age 10 days: 2.5 µg/kg^{1.5} per hour; age 11 days to 1 year: 5 µg/kg^{1.5} per hour) or paracetamol (30 mg/kg/day in 4 doses). For patients randomized to paracetamol, a placebo normal saline infusion was used, whereas normal saline was administered in four separate doses for patients randomized to morphine. Morphine was also administered as needed (10 days: 10 µg/kg; 11 days to 1 year: 15 µg/kg) to patients in both groups when pain scales (Numeric Rating Scale-11 and COMFORT-Behavior Scale) indicated pain. Following three “rescue” doses, if the patient was still in pain, a continuous morphine infusion was initiated. The primary outcome was cumulative morphine dose (study and rescue), whereas secondary outcomes were pain scores and adverse effects. The cumulative morphine dose during the first 48 post-operative hours were 357 (n=38; interquartile range 220–605) µg/kg and 121 (n=33; interquartile range 99–264) µg/kg in the morphine and paracetamol groups (P<0.001), respectively. No significant differences were noted in pain scores or adverse effects between groups. The authors concluded that intermittent use of paracetamol lowered the 48-hour cumulative morphine dose when compared to use of a continuous morphine infusion [80].

CONCLUSION

In the United States, passage of the FDASIA legislation made BPCA and PREA permanent, no longer requiring reauthorization every 5 years. This landmark legislation also stressed the importance of performing clinical trials in neonates when appropriate. In Europe, the Pediatric Regulation, which went into effect in early 2007, also provides a framework for expanding pediatric clinical research. Although much work remains, as a result of greater regulatory guidance, more pediatric data are reaching product labels.

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KEY POINTS

- Pediatric research has expanded in the United States and Europe largely due to legislation providing a framework for the design and execution of pediatric studies.
- Although much work remains, as a result of greater regulatory guidance, more pediatric data are reaching product labels.
- The pharmacokinetic/pharmacodynamic properties of many drugs used to treat children have yet to be characterized.

Table 1

Select drug label changes made by U.S. Food and Drug Administration in 2012 and 2013

Generic Name	Trade Name	Indication Studied	Summary of Label Change(s)
Azelastine	Astepro® nasal spray	Treatment of perennial and seasonal allergic rhinitis	Expanded indication to include pediatric patients 6 years of age
Beclomethasone dipropionate	QNASL™	Treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis	Safety and efficacy established in pediatric patients 12 years of age
Dexmedetomidine hydrochloride	Precedex™	Sedation in intubated and mechanically ventilated patients	Safety and effectiveness for procedural or intensive care unit sedation is not established in pediatric patients
Dolutegravir	Tivicay®	Treatment of HIV-1 infection	Indicated in combination with other antiretroviral drugs in children 12 years of age and weighing 40 kg
Duloxetine hydrochloride	Cymbalta®	Treatment of major depressive disorder (MDD)	Efficacy was not established in two 10-week, placebo-controlled trials of 800 patients with MDD 7–17 years of age
Enravirine	Intelence®	Treatment of HIV-1 in treatment experienced patients with other anti-retroviral drugs	Expanded indication to include pediatric patients 6 years of age
Eszopiclone	Lunesta®	ADHD associated with insomnia	Safety and effectiveness have not been established in pediatric patients
Fluticasone/salmeterol	Advair HFA®	Treatment of asthma	Safety and effectiveness have not been established in children <12 years of age
Fosamprenavir	Lexiva®	Treatment of HIV-1 infection	Expanded indication to include pediatric patients 4 weeks to <2 years of age
Iron sucrose	Venofer®	Treatment of iron deficiency anemia in patients with chronic kidney disease	Expanded indication from adults to pediatric patients 2 years of age
Ivermectin	Sklice®	Topical treatment of head lice infestations	Safety and efficacy established in children 6 months of age
Lisdexamfetamine	Vyvanse™	Maintenance treatment of ADHD	Approved for treatment of ADHD in patients aged 6–17 years
Micafungin sodium	Mycamine®	Treatment and prophylaxis of <i>Candida</i> infections	Safety and effectiveness demonstrated in pediatric patients 4 months of age
Montelukast	Singulair® oral granules, tablets, and chewable tablets	Prevention of exercise-induced bronchoconstriction	Expanded indication to include pediatric patients 6–14 years of age
Nevirapine	Viramune XR®	Treatment of HIV-1 infection	Approved for use as treatment for HIV-1 infection with other antiretroviral agents in children 6 to <18 years of age
Olanzapine and fluoxetine	Symbyax®	Treatment of depressive episodes associated with bipolar I disorder	Expanded indication to include pediatric patients age 10–17 years
Oxcarbazepine	Oxtellar XR™	Adjunctive therapy of partial seizures	Safety and effectiveness for treatment of partial-onset seizures is

Generic Name	Trade Name	Indication Studied	Summary of Label Change(s)
Perampanel	Fycompa™	Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy	established in pediatric patients 6–16 years of age
Rabeprazole	Aciphex®	Gastroesophageal reflux	Expanded indication to pediatric patients 1 years of age
Retapamulin	Altabax®	Treatment of impetigo	Use not indicated in patients <9 months of age
Sildenafil	Revatio®	Treatment of pulmonary hypertension	Warning added: “Use of Revatio, particularly chronic use, is not recommended in children.”
Tenofovir disoproxil fumarate	Viread®	Treatment of chronic hepatitis B	Expanded indication from adults to include pediatric patients 12 to <18 years of age
Tenofovir disoproxil fumarate	Viread®	Treatment of HIV infection in combination with other antiretroviral agents	Expanded indication from adults to include pediatric patients 2 to <12 years of age, weighing 17 kg, and who can swallow an intact tablet

* Data populating this table was taken from the FDA Pediatric Labeling Information Database. Accessed via: <http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>.

Table 2

Recently published pediatric pharmacokinetic studies of anti-infective agents

Drug	Patient Population	PK Analysis Approach	Dosing Modifications Recommended for Studied Population (yes/no)
<i>Antimicrobials</i>			
Daptomycin [33]	Infants	Non-compartmental	Yes
Daptomycin [34]	Infants and children	Descriptive	Yes
Metronidazole [35]	Preterm infants	Population	Yes
Tigecycline [36]	Children	Non-compartmental	Yes
Vancomycin [37]	Neonates	Population	Yes
Vancomycin [38]	Children <18 years	Population	Yes
<i>Antifungals</i>			
Fluconazole [39]	Infants	Individual, compartmental	Yes
Micafungin [40]	Infants, children and adolescents	Non-compartmental	No
Voriconazole [41]	Children, adolescents, and adults	Population	Yes
<i>Antivirals</i>			
Abacavir [42]	Infants and toddlers	Population	Yes
Acyclovir [43]	Preterm and term infants	Population	Yes
Darunavir/ritonavir [44]	Children	Non-compartmental	No
Etravirine [45]	Children and adolescents	Non-compartmental	Yes
Oseltamivir [46]	Neonates and infants	Population	Yes
Tenofovir [47]	Children and adolescents	Population	No
Valganciclovir [48]	Infants and children	Non-compartmental	Yes
<i>Antimalarials</i>			
Artesunate [49]	Infants and children	Population	Yes