Given patient. The utility of this approach for individualizing treatment with codeine is described by a recent Clinical Pharmacogenetics Implementation Consortium guideline. Incorporation of pharmacogenomic data for polymorphically expressed genes regulating the expression of drug metabolizing enzymes and, potentially, drug transporters, into an allometric approach to assess pharmacokinetics or drug regimen selection in pediatric patients would be expected to increase predictive accuracy of the models.

CONCLUSION

Historically, pharmacokinetic investigations conducted in pediatric patients have ignored the potential effects of the interaction between disease expression, nutritional status, and the effects of concurrent therapy on drug disposition. The incorporation of allometric principles as they relate body size to the multiple factors that influence drug disposition can markedly enhance the ability to predict drug clearance and, thus, individualize drug therapy in a given child. However, to do this successfully the intersection of disease expression (acute or chronic), changes in body composition at the extremes of body size, and pharmacogenetic constitution must be considered. Only then can the promise of “precision medicine” be realized in pediatrics.

ACKNOWLEDGMENTS

The author gratefully acknowledges the contribution of Dr Susan Abdel-Rahman, whose thoughts on the prediction of body size and its relationship to drug disposition were illuminating. This work is supported in part by funding received by the author through his participation in the Pediatric Trial Network (HHSN275201000003I) and a training grant (1T32HD069038-01) funded by the Eunice Kennedy Shriver National Institute of Child Health, National Institutes of Health, Bethesda, MD.

CONFLICT OF INTEREST

Dr Kearns has no conflicts of interest to disclose as relates to the information contained in the article.

© 2015 ASCPT


Challenges in Childhood Tuberculosis

S. Swaminathan and G. Ramachandran

While tuberculosis (TB) typically causes respiratory disease in adults, the spectrum of disease is different in children, ranging from paucibacillary lymphadenitis or limited intrathoracic disease to severe disseminated disease. Diagnosing pediatric TB and monitoring treatment response is challenging, as collecting respiratory specimens is difficult in children and disease may be extrapulmonary. While basic principles of treatment are similar to adults, developmental differences in pharmacokinetics and pharmacodynamics require that drug dosages in children be adjusted for body weight and age.

1National Institute for Research in Tuberculosis, Chennai, India. Correspondence: S Swaminathan (doctorsoumya@yahoo.com, soumysas@mirt.res.in)
doi:10.1002/cpt.175
In the absence of pharmacodynamic data in children, adult data that demonstrated an association between serum drug concentration and clinical outcome has been used to arrive at targeted serum drug concentrations for all anti-TB drugs. Doses for children are largely extrapolated from adult pharmacokinetic studies. However, in children physiological changes that occur with growth and development cause differences in absorption, distribution, metabolism, and excretion of drugs. Several age-related factors, including gastric acid secretion, gastric emptying time, intestinal transit time, and gastrointestinal motility influence absorption of drugs in children. Body composition and tissue binding characteristics vary greatly with age and play a major role in the distribution of drugs. Maturation of hepatic enzyme activity in children has a profound effect on drug levels, implying that dosing recommendations should be based on age and/or body surface area.

### PHARMACOKINETIC STUDIES

The influence of developmental changes on the pharmacokinetics of anti-TB drugs in children and its impact on treatment outcomes has been recognized relatively recently. While response to treatment depends on multiple factors, subtherapeutic serum concentrations of drugs could potentially lead to unsatisfactory treatment outcomes. Drug concentrations are influenced by several factors such as age, ethnicity/genetic factors, nutritional status, human immunodeficiency virus (HIV) infection, drug–drug interactions, drug–food interactions, etc. **Table 1** shows the wide variability in peak concentrations of different anti-TB drugs, in various studies, highlighting the generally low, suboptimal levels achieved.

### Age

Drug therapy in infancy and childhood requires special dose considerations; changes are most rapid from birth to 2 years of age and slow down thereafter. Consequently to studies reporting that young children require higher mg/kg doses of anti-TB drugs to achieve the same drug concentrations as in adults, the WHO revised pediatric dosages: RMP from 10 mg/kg to 15 mg/kg, INH from 5 mg/kg to 10 mg/kg, and PZA from 25 mg/kg to 35 mg/kg. While a recent study from South Africa found that concentrations of first-line anti-TB drugs were markedly below the target therapeutic concentrations in most children who received the revised WHO-recommended pediatric weight-based dosages, these revised doses were

---

**Table 1**  Peak concentrations of anti-TB drugs from recent studies in children

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Venezuela (geometric mean &amp; range) µg/ml</th>
<th>India (median &amp; IQR) µg/ml</th>
<th>South Africa (PK model-derived peak conc.) median (range); mg/L</th>
<th>Malawi (median &amp; IQR) µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–3 years</td>
<td>3.1–6 years</td>
<td>6.1–9 years</td>
<td>9.1–12 years</td>
</tr>
<tr>
<td>RMP</td>
<td>5.1 (1.5–13.6)</td>
<td>3.1 (2.4–4.0)</td>
<td>5.5 (4.4–6.6)</td>
<td>7.0 (4.2–7.7)</td>
</tr>
<tr>
<td>INH</td>
<td>1.9 (0.7–5.2)</td>
<td>3.3 (2.4–4.6)</td>
<td>6.1 (3.1–8.4)</td>
<td>6.3 (4.4–9.0)</td>
</tr>
<tr>
<td>PZA</td>
<td>31.5 (10.3–71.7)</td>
<td>30.4 (26.2–33.4)</td>
<td>38.5 (31.4–44.2)</td>
<td>40.9 (38.3–47.4)</td>
</tr>
<tr>
<td>EMB</td>
<td>1.8 (0.9–3.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Ref #** 7

**THERAPEUTIC GUIDELINES**

**Table 1** shows the wide variability in peak concentrations of different anti-TB drugs, in various studies, highlighting the generally low, suboptimal levels achieved.

---

**TREATMENT**

The basic principles of treatment and recommended standard anti-TB regimens for children are similar to those for adults. For children with drug-sensitive TB, a four-drug regimen with isoniazid (INH), RMP, pyrazinamide (PZA), and ethambutol (EMB) for 2 months (intensive phase), followed by INH and RMP for 4 months (continuation phase), is recommended. Treatment should be given daily in the intensive phase at least, and may be extended up to 9–12 months in severe forms of TB. Dosages of first-line anti-TB drugs were revised by the World Health Organization (WHO) in 2010. Because TB is generally paucibacillary in nature in children, it may be possible to further shorten chemotherapy, but this needs testing in clinical trials.

In the absence of pharmacodynamic data in children, adult data that demonstrated an association between serum drug concentration and clinical outcome has been used to arrive at targeted serum drug concentrations for all anti-TB drugs. Doses for children are largely extrapolated from adult pharmacokinetic studies. However, in children physiological changes that occur with growth and development cause differences in absorption, distribution, metabolism, and excretion of drugs. Several age-related factors, including gastric acid secretion, gastric emptying time, intestinal transit time, and gastrointestinal motility influence absorption of drugs in children. Body composition and tissue binding characteristics vary greatly with age and play a major role in the distribution of drugs. Maturation of hepatic enzyme activity in children has a profound effect on drug levels, implying that dosing recommendations should be based on age and/or body surface area.

---

**PHARMACOKINETIC STUDIES**

The influence of developmental changes on the pharmacokinetics of anti-TB drugs in children and its impact on treatment outcomes has been recognized relatively recently. While response to treatment depends on multiple factors, subtherapeutic serum concentrations of drugs could potentially lead to unsatisfactory treatment outcomes. Drug concentrations are influenced by several factors such as age, ethnicity/genetic factors, nutritional status, human immunodeficiency virus (HIV) infection, drug–drug interactions, drug–food interactions, etc. **Table 1** shows the wide variability in peak concentrations of different anti-TB drugs, in various studies, highlighting the generally low, suboptimal levels achieved.

---

**Age**

Drug therapy in infancy and childhood requires special dose considerations; changes are most rapid from birth to 2 years of age and slow down thereafter. Consequently to studies reporting that young children require higher mg/kg doses of anti-TB drugs to achieve the same drug concentrations as in adults, the WHO revised pediatric dosages: RMP from 10 mg/kg to 15 mg/kg, INH from 5 mg/kg to 10 mg/kg, and PZA from 25 mg/kg to 35 mg/kg. While a recent study from South Africa found that concentrations of first-line anti-TB drugs were markedly below the target therapeutic concentrations in most children who received the revised WHO-recommended pediatric weight-based dosages, these revised doses were...
### Table 2  Current status, challenges, and research priorities

<table>
<thead>
<tr>
<th>Epidemiology</th>
<th>Current status</th>
<th>Challenges</th>
<th>Priority studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated 550,000–1,000,000 children with TB each year (modeling studies). Estimated 30,000 children with DRTB each year (modeling)</td>
<td>Children excluded from most prevalence surveys. Assumptions made for estimation of TB in adults may not be valid in children. Lack of recognition of fact that proportion of MDR-TB in children similar to proportion in treatment naive adults in same setting</td>
<td>Studies to estimate the burden of pediatric TB—from notification data, capture-recapture studies or prevalence surveys Household contact investigations of TB and DRTB patients could improve the early detection of pediatric TB</td>
</tr>
</tbody>
</table>

### Diagnosis

| Collection of specimens       | Gastric aspirates, induced sputum, nasopharyngeal aspirates, and fine needle aspiration biopsy are standard | All these procedures need good facilities and trained staff. Airborne infection control needed for induced sputum. Procedures not done in peripheral settings. Need a diagnostic test for TB which can be applied to blood, urine, or saliva | To explore other specimens from children (saliva, urine, stool, etc.) for diagnostic testing |

| Newer diagnostics            | Cartridge based nucleic acid amplification test (Xpert MTB/Rif) has improved detection of MTB in children. Fluorescence microscopy not very useful | Xpert MTB/RIF: cartridge cost, limited availability, needs adequate specimens, and has suboptimal sensitivity in children. Next generation Xpert and many fast followers coming up. Need a test that differentiates latent TB infection from active TB | Biomarker studies enrolling cohorts of children with confirmed, probable, and possible TB, as well as children without TB infection/disease. Optimal combinations of biomarkers, once validated, can be made into a point-of-care test |

### Treatment

| Drug-sensitive TB             | New treatment recommendations from WHO: 6-month daily treatment with revised drug dosages. Treatment extended to 12 months for serious forms of TB | Role of ethambutol in continuation phase is not well defined, not contained in fixed-dose combination preparations. Existing quality assured pediatric formulations not according to revised WHO dosing | Clinical trials of a) shorter regimens for uncomplicated TB, b) more effective regimens for disseminated and severe forms of TB, c) optimizing the dose of various first and second line anti-TB drugs across the age range of children (0–18 years) |

| Drug-resistant TB             | Outcomes in children with MDR-TB are very good, when treated appropriately | Few children treated in existing MDR treatment programs; substantial side effects, especially ototoxicity with injectable use. Quality assured pediatric second line drugs not available | Expand drug susceptibility testing in children and include them in drug resistance surveys Test fully oral and shorter MDR TB regimens Explore the role of host directed therapies in improving outcomes |

| TB-HIV coinfection           | Prevention of mother to child transmission programs expanding, lower numbers of pediatric HIV; early initiation of ART in all HIV-infected children regardless of CD4 count | Outcomes of TB/HIV treatment poor. Malabsorption and reduced bioavailability of drugs described. Role of ethambutol in all children with TB-HIV not well defined, adds to pill burden. Treatment of <3 years children with TB/HIV challenging, need to consider ART adjustment when coadministering protease inhibitors and rifampicin | Clinical trials of newer anti-retroviral regimens compatible with rifampicin use Optimal dose of rifabutin for children receiving protease inhibitors |

| Pharmacokinetics             | Sparse pharmacokinetic data about first-line and second-line TB drugs in children; some studies ongoing | Data are mostly from South Africa and India. Modeling studies are showing that young children need much higher doses of rifampicin than currently administered, especially in conditions like meningitis | Drug-drug interaction studies and pharmacokinetic studies with newer anti-retrovirals PK of anti-TB drugs in CSF and optimizing dosages to treat meningitis |

### Prevention

| Preventing airborne transmission | Greater risk awareness and improved guidelines for airborne | Poor implementation in most TB endemic countries; many | |
reported to be adequate in some other studies. Among Indian children treated with intermittent regimens, children below 3 years had significantly lower peak concentration and exposure of RMP, INH, and PZA than those above 3 years, despite receiving similar drug doses on a mg/kg basis.

Nutritional status
The pathophysiological changes associated with malnutrition can alter pharmacokinetic processes, drug responses, and toxicity. Poor nutritional status could cause malabsorption of drugs, alter levels of hepatic drug-metabolizing enzymes, and enhance renal clearance, thus decreasing drug concentrations. Blood concentrations of RMP, INH, PZA, and EMB have been shown to be reduced in malnourished children.

HIV infection
While HIV influences TB outcome in different ways, the inability to achieve and sustain therapeutic levels of anti-TB drugs (possibly due to malabsorption) could be a major factor in causing poor treatment outcomes. Because it is clear that concomitant treatment of HIV infection in coinfected children reduces morbidity and mortality, highly active antiretroviral treatment should be initiated a few weeks after anti-TB treatment (ATT). In view of RMP being a potent inducer of the hepatic microsomal enzyme system, drug interactions occur with protease inhibitors and nevirapine; efavirenz is the drug of choice. However, for children below 3 years, appropriate dosing of efavirenz has not been determined. Treatment of coinfection children in this age group is a challenge, the options being to use a higher dose of nevirapine or a triple nucleoside reverse transcriptase inhibitor regimen. There is an urgent need for studies of efficacy and safety of different drug combinations of antiretroviral and anti-TB drugs (including the new drugs) in children.

CLINICAL TRIALS
Performing clinical trials of anti-TB drugs in children is challenging because of uncertainty of diagnosis in the majority of cases, the lack of accurate surrogate markers of treatment response, and the lack of child-friendly formulations. The major limitation in performing treatment trials in children is the lack of a definitive gold standard for diagnosis and monitoring response. Monitoring of treatment response is usually based on symptomatic improvement, weight gain, and regression of radiographic lesions, although specimens should be collected for Mycobacterium tuberculosis culture, wherever possible. In the absence of microbiological positivity in the majority of cases, there is a need for a surrogate marker for response to treatment.

Very few clinical trials have been performed to test the efficacy of various regimens in children and most results are extrapolated from adult studies. While this is reasonable for the majority of pulmonary TB patients, trials are needed to improve treatment outcomes in young children with severe/disseminated TB. For example, a trial is planned to test the safety and efficacy of high-dose RMP and levofloxacin in the management of TB meningitis in children. At the other end of the spectrum are children with minimal disease, who can probably be treated with shorter and simpler regimens. The SHINE multicountry trial will test the efficacy of a 4-month regimen using the new WHO-recommended dosages, in uncomplicated intrathoracic TB in children.

A further issue that needs attention is making pediatric formulations available: both individual and fixed dose combination tablets with good bioavailability. The need is especially great for second-line drugs, where there are hardly any pediatric formulations available. In the growing pipeline of potential new TB drugs, there are several novel compounds in various stages of clinical development, including the fluoroquinolones, bedaquiline, delamanid, and PAR24 (premanid). In order to advance drug development and improve access to new drugs, it is suggested that phase II safety and dose-finding studies be initiated in children as soon as safety and preliminary efficacy has been established in adults.

MULTIDRUG-RESISTANT (MDR) TB
Management of MDR TB in children is a challenge, because it requires prolonged treatment with more toxic and less efficacious second-line drugs (including an injectable for 6 months). In general, a child with MDR TB will need to take 4–5 oral drugs for 18–24 months plus an injectable for 6 months. The high pill burden is further complicated by the fact that pediatric

Table 2 Continued

<table>
<thead>
<tr>
<th>Current status</th>
<th>Challenges</th>
<th>Priority studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive therapy/chemoprophylaxis</td>
<td>Preventive therapy recommended for all children &lt; 5 years in contact with smear positive pulmonary TB and in all HIV+ children &gt; 1 year. Simple symptom-based screening to rule out TB</td>
<td>Implementation weak; not included in monitoring and assessment activities; potential benefit of continuous isoniazid preventive therapy in children remains unclear; higher priority needs to be accorded by national TB control programs</td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; MDR, multidrug-resistant; MTB, Mycobacterium tuberculosis; RIF, rifampicin; TB, tuberculosis.
formulations are lacking for most second-line drugs, and tablets have to be crushed or broken and administered. Despite these challenges, children with MDR TB have good treatment outcomes, if treated appropriately. MDR TB in children is often not diagnosed or diagnosed late, leading to unnecessary mortality and morbidity. A high index of suspicion is required as well as good clinical judgment, as in many cases the diagnosis will be one of “probable MDR TB,” in the absence of bacteriologic confirmation. Household child contacts of MDR TB patients carry a high risk of contracting active TB and MDR TB disease and constitute a high-risk group. There is limited information on optimal treatment of latent TB infection in children in contact with patients with MDR TB. Multicentric trials are needed to determine the most effective drug combination and optimal duration of chemoprophylaxis for contacts of patients with MDR TB.

RESEARCH NEEDS
Progress on several aspects of childhood TB has been made in the recent past. Issues related to disease burden, diagnosis, treatment, and prevention have been addressed, but key challenges still remain (Table 2). Well-designed, adequately powered multicentric studies are needed to design optimal treatment and prevention strategies for children with TB and MDR TB.

CONFLICT OF INTEREST/DISCLOSURE
The authors declare no conflicts of interest.

© 2015 ASCPT