given patient.[9] The utility of this approach for individualizing treatment with codeine is described by a recent Clinical Pharmacogenetics Implementation Consortium guideline.[10] 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.

1. Kearns, G.L. *et al*. Developmental pharmacology—drug disposition, action and therapy. *N. Engl. J. Med.* **18**, 1157–1167 (2003).
2. Holford, N. Dosing in children. *Clin. Pharmacol. Ther.* **87**, 367–370 (2010).
3. Anderson, B.J. & Holford, N.H.G. Tips and traps analyzing pediatric PK data. *Pediatr. Anesth.* **21**, 222–237 (2011).
4. Kleiber, M. Body size and metabolic rate. *Physiol. Rev.* **27**, 511–541 (1947).
5. Russell, J. *et al*. Altered energy metabolism in anorexia nervosa. *Psychoneuroendocrinology* **26**, 51–63 (2001).
6. Brion, L.P., Boeck, M.A., Gauthier, B., Nussbaum, M.P. & Schwartz, G.J. Estimation of glomerular filtration rate in anorectic adolescents. *Pediatr. Nephrol.* **3**, 16–21 (1989).
7. Chikamori, K. *et al*. Distribution volume, metabolic clearance and plasma half disappearance time of exogenous lutenizing hormone releasing hormone in normal women and women with obesity and anorexia nervosa. *Acta Endocrinol. (Copenh.)* **96**, 1–6 (1981).
8. Tolbert, J. & Kearns, G.L. The challenge of obesity in paediatric leukaemia treatment: it is not just size that matters. *Arch. Dis. Child.* **100**, 101–105 (2015).
9. Gaedigk, A. *et al*. The CYP2D6 activity score: translating genotype information in a qualitative measure of phenotype. *Clin. Pharmacol. Ther.* **83**, 234–242 (2008).
10. Crews, K.R. *et al*. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin. Pharmacol. Ther.* **95**, 376–382 (2014).

Challenges in Childhood Tuberculosis

S. Swaminathan[1] and G. Ramachandran[1]

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.

DIAGNOSIS

There has been limited progress on improving the diagnosis of TB in children—an ideal test should work on saliva, urine, or blood rather than sputum or respiratory secretions, differentiate TB infection from disease, and be rapid (preferably point-of-care), sensitive, and specific. Several studies have shown that the Xpert MTB/RIF (Cepheid, Sunnyvale, CA) detects significantly more cases than smear microscopy using sputum or gastric lavage, and is highly specific, but sensitivity is less than culture. Another advantage of Xpert MTB/RIF is the rapid detection of rifampicin (RMP) resistance, which enables the start of optimal treatment, weeks ahead of standard culture-based drug sensitivity testing. A recent systematic review and meta-analysis by Detjen *et al*.[1] observed that,

[1]National Institute for Research in Tuberculosis, Chennai, India. Correspondence: S Swaminathan (doctorsoumya@yahoo.com, soumyas@nirt.res.in)
doi:10.1002/cpt.175

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

Drugs	Venezuela (geometric mean & range) μg/ml	India (median & IQR) μg/ml				South Africa (PK model-derived peak conc.) median (range); mg/L	Malawi (median & IQR) μg/ml
		1–3 years	3.1–6 years	6.1–9 years	9.1–12 years		
RMP	5.1 (1.5–13.6)	3.1 (2.4–4.0)	5.5 (4.4–6.6)	7.0 (4.2–7.7)	5.9 (4.1–7.1)	3.47 (0.56–10.20)	2.9 (2.1–3.4)
INH	1.9 (0.7–5.2)	3.3 (2.4–4.6)	6.1 (3.1–8.4)	6.3 (4.4–9.0)	7.2 (5.6–8.5)	6.05 (1.83–10.28)	3.4 (2.6–4.6)
PZA	31.5 (10.3–71.7)	30.4 (26.2–33.4)	38.5 (31.4–44.2)	40.9 (38.3–47.4)	38.0 (30.1–45.1)	22.51 (11.18–47.17)	34.6 (32.3–40.9)
EMB	1.8 (0.9–3.7)					1.44 (0.62–6.28)	1.2 (0.8–1.7)
Ref #	7	8				5	

Therapeutic ranges of peak concentrations: RMP: 8–24 μg/ml; INH: 3–6 μg/ml; PZA: 35–60 μg/ml; EMB: 2–5 μg/ml.
Doses used in the studies: Venezuela: Daily RMP: 10 mg/kg; INH: 5 mg/kg; PZA: 25 mg/kg; EMB: 15 mg/kg.
India: Thrice weekly RMP & INH: 10 mg/kg; PZA: 30–35 mg/kg; EMB: 30 mg/kg.
South Africa: Daily RMP & INH: 10–15 mg/kg; PZA: 30–40 mg/kg; EMB: 15–25 mg/kg.
Malawi: Daily RMP: 10 mg/kg; INH: 5 mg/kg; PZA: 25 mg/kg; EMB: 20 mg/kg.

compared with culture, the pooled sensitivities and specificities of Xpert for TB detection were 62% and 98%, respectively, with the use of expectorated or induced sputum samples and 66% and 98%, respectively, with the use of samples from gastric lavage. Xpert sensitivity in culture-negative children started on anti-TB therapy was 2% for expectorated or induced sputum. Xpert's pooled sensitivity and specificity to detect RMP resistance was 86% and 98%, respectively.[1] Despite the significant improvement in rates of bacteriologic confirmation with Xpert, at least a third of pulmonary TB in children is based on clinical and radiographic findings. Further, advances in imaging techniques (e.g., positron emission tomography/computed tomography (PET-CT) scans) are revealing that TB infection is a spectrum, with evidence of metabolically active lung granulomas in persons with latent TB infection, in the absence of any symptoms or radiographic findings. While several studies have shown that CT is more sensitive than chest radiography, it cannot be recommended as a routine diagnostic test because of radiation exposure and cost concerns.

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.[2]

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. Consequent 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

	Current status	Challenges	Priority studies
Epidemiology	Estimated 550,000–1,000,000 children with TB each year (modeling studies). Estimated 30,000 children with DRTB each year (modeling)	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 MDRTB in children similar to proportion in treatment naïve adults in same setting	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
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 coadministrating protease inhibitors and rifampicin	Clinical trials of newer antiretroviral 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 antiretrovirals 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	

Table 2 ***Continued***

	Current status	Challenges	Priority studies
	infection control—both in clinics and in the community	opportunities for nosocomial transmission to children, including hospital waiting rooms and maternity wards	Better models for prevention of transmission in households/ community
Preventive therapy/ chemoprophylaxis	Preventive therapy recommended for all children < 5 years in contact with smear positive pulmonary TB and in all HIV+ children > 1 year. Simple symptom-based screening to rule out TB	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	Clinical trials of a) safety and tolerability of new short-course preventive therapy regimens, b) better vaccines for prevention of TBc Other approaches, e.g., micronutrient supplementation, Vitamin D for prevention

ART, antiretroviral therapy; MDR, multidrug-resistant; MTB, *Mycobacterium tuberculosis*; RIF, rifampicin; TB, tuberculosis.

reported to be adequate in some other studies.[3–5] 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.[6]

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.[7]

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.[8] 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 coinfected 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 PA824 (pretomanid). 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.[9]

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

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.[10] 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.

1. Detjen, A.K. *et al*. Xper MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: A systematic review and meta-analysis. *Lancet Respir. Med.* **3**, 451–461 (2015).
2. Kearns, G.L. *et al*. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N. Engl. J. Med.* **349**, 1157–1167 (2003).
3. Hiruy, H. *et al*. Subtherapeutic concentrations of first-line anti-TB drugs in South African children treated according to current guidelines: the PHATISA study. *J. Antimicrob. Chemother.* **70**, 1115–1123 (2015).
4. Thee, S. *et al*. Pharmacokinetics of isoniazid, rifampin and pyrazinamide in children younger than two years of age with tuberculosis: Evidence for implementation of revised world health organization recommendations. *Antimicrob. Agents Chemother.* **55**, 5560–5567 (2011).
5. Verhagen, L.M. *et al*. Pharmacokinetics of anti-tuberculosis drugs in Venezuelan children younger than 16 years of age: Supportive evidence for the implementation of revised WHO dosing recommendations. *Trop. Med. Int. Health.* **17**, 1449–1456 (2012).
6. Ramachandran, G. *et al*. Age, nutritional status and isoniazid acetylator status influence pharmacokinetics of anti-TB drugs in children. *Int. J. Tuberc. Lung Dis.* **17**, 979–984 (2013).
7. Graham, S.M. *et al*. Low levels of pyrazinamide and ethambutol in children with tuberculosis and impact of age, nutritional status and human immunodeficiency virus infection. *Antimicrob. Agents Chemother.* **50**, 407–413 (2006).
8. Manosuthi, W. & Wongsawat, J. Treatment challenges in co-infected HIV and TB children. *Indian Pediatr.* **48**, 937–938 (2011).
9. Nachman, S. *et al*. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. *Lancet Infect. Dis.* **15**, 711–720 (2015).
10. Ettehad, D., Schaaf, H.S., Seddon, J.A., Cooke, G.S. & Ford, N. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infect. Dis.* **12**, 449–456 (2012).