ABSTRACT • The diagnosis of hypertension in children relies upon blood pressure distribution tables adjusted for gender, age, and height. Unlike in adults, specific blood pressure levels corresponding to long-term adverse outcomes in children have not been established. However, there are known surrogate markers of target organ injury associated with elevated blood pressure, such as left ventricular hypertrophy, retinal changes, thickening of the carotid artery wall, cognitive changes, and even evidence of early atherosclerosis. Moreover there is corroboration that hypertension in children predicts adult hypertension. In view of the global childhood obesity epidemic, in conjunction with the well-established association of obesity and hypertension, evaluation of blood pressure in the pediatric population has become an important health concern. With this insight, efforts continue worldwide to accurately measure, determine prevalence and monitor recent trends of hypertension in children and adolescents.

INTRODUCTION
Hypertension (HT) is a leading cause of adult morbidity and mortality worldwide. It is estimated to affect approximately 1 billion persons globally, and accounts for 7 million deaths yearly [1-2]. In adults, HT is well known as an independent risk factor for cardiovascular disease [1]. In children and adolescents blood pressure (BP) levels at which long-term cardiovascular risk increases have not been well established. Regardless, HT in children and adolescents is the focus of numerous studies that have examined intermediate measures of target organ injury as well as BP tracking into adulthood. Of recent interest in pediatric HT is the attempt to accurately determine prevalence and establish secular trends, especially given the well-documented association of BP with body mass index (BMI) in children [2-5] and the marked increase in prevalence of childhood adiposity worldwide [6-11]. Several studies in the United States have demonstrated increases in mean BP and prevalence of HT, trends that are in part attributable to the increased prevalence of obesity. However, worldwide data has shown variable trends in BP and HT in children, making it difficult to ascertain the true prevalence of the condition and the impact of the epidemic of obesity on BP. The purpose of this review is to discuss the epidemiology of HT in children and adolescents, including factors that influence its prevalence and known outcome measures of pediatric HT.

PREVALENCE OF HYPERTENSION
There is increasing interest in the various epidemiologic aspects of BP, specifically with regard to trends in mean BP levels, trends in the prevalence of HT; and associations between suspected risk factors and high BP. Additionally, the breadth of data on the topic is expanding worldwide. Large-scale BP surveys have been used to accurately estimate prevalence of HT, but interpretation and comparison of the data is complicated by several methodological limitations [2, 12]. One such limitation arises from the definition used for HT, another the region in which the study

Christopher LaRosa, Kevin Meyers


RÉSUMÉ • Le diagnostic de l'hypertension chez l'enfant se base sur les courbes de pression artérielle ajustées en fonction du sexe, de l'âge et de la taille. À l'enceinte de l'adulte, les niveaux de pression artérielle correspondant à des effets nuisibles à long terme n'ont pas été établis chez l'enfant. Cependant, il existe des marqueurs connus témoignant de la présence de lésions au niveau des organes cibles, associés à une élévation de la pression artérielle, comme l'hypertrphie ventriculaire gauche, les changements rétinens, l'épaississement de la paroi de l’artère carotide, les changements cognitifs, et même l'évidence d'une athérosclérose précoce. En outre, il existe une confirmation que l'hypertension chez l'enfant prédit la survenue de l'hypertension chez l'adulte. En raison de l'épidémie globale d’obésité chez l'enfant, et en conjonction avec l'association bien établie entre obésité et hypertension, l'évaluation de la pression artérielle dans la population pédiatrique est devenue un important problème de santé. Au vu de ces données, des efforts continus sont entrepris à l'échelle mondiale pour mesurer avec précision, déterminer la prévalence et surveiller les nouvelles tendances de l'hypertension chez l'enfant et l'adolescent.

takes place. BP definition varies worldwide, as does the body of normative data that has been collected from various populations. The most widely used definition was published by the National High Blood Pressure Education Program (NHBPEP) Working Group’s Fourth Report [13], and it provides age and height-adjusted BP tables for boys and girls. Using these tables, prehypertension is defined as an average BP ≥ 90th percentile and < 95th or in adolescents as the adult definition of ≥ 120/80 mmHg. Hypertension exists when the mean systolic or diastolic BP is ≥ 95th percentile on ≥ 3 occasions. In 2007, BP curves were derived from analysis of seven nationally representative BP data surveys in the UK, which showed that BP increased progressively with age, with the most rapid increase occurring during puberty [14]. Age-adjusted BP from this survey had a greater association with weight than height, particularly SBP. These oscillometric data gave rise to the definition of high and high-normal BP for children in Great Britain as above the 98th percentile and between the 91st and 98th percentile, respectively. Similarly, the Nord-Tronndelag Health Study II provided reference BP tables for adolescents in Northern Europe using an oscillometric device [15]. Interestingly, these data showed a consistently higher range of BP values across percentiles when compared to both UK and US normative data, suggesting that updated region-specific BP tables should be formulated.

A recent study done with 839 Southern Italian adolescents using sphygmomanometer readings showed a significant overestimation of the prevalence of HT when applying US blood pressure tables compared with Sardinian distribution curves (p < 0.00001) [16].

Many international studies have used the NHBPEP definition for HT, but have applied inconsistent methods for generating data sets [2]. The methodological variation among these studies arises from differences in the number of measurements done in a single visit, the use of measurements from subsequent visits, and the equipment used. Percentages derived from one BP reading will vary from those that average three readings or those that perform multiple sets of readings during separate encounters. The NHBPEP definition of HT requires that measurements are made on three separate occasions to account for an accommodation effect and the statistical phenomenon of regression toward the mean [13]. Use of multiple readings provides lower estimates of HT prevalence, and therefore a lack of standardization in BP measurement among studies often precludes the ability to reliably compare data. The instrument used for BP measurement also obscures the data because oscillometric devices vary by manufacturer and require validation and calibration. Alternatively, auscultation is subject to operator-dependent biases such as rounding errors (digit preference), expectation bias, and operator skill. Of note, the NHBPEP recommends that all elevated BP levels taken by an automated device be repeated manually using Korotkoff 5 (K5) as the DBP. Recent studies have challenged the use of K5 for DBP, reporting that automated devices or use of K4 provide improved BP tracking [17].

A reliable estimate of the worldwide prevalence of HT is not currently feasible. Lack of outcome data in children prevents a universal definition, and due to international variation in BP data it has been emphasized that BP definitions be determined regionally [15-16]. Using the 1996 U.S. Task Force criteria, worldwide prevalence estimates ranged from < 1% to 5.1% [18].

A literature review was undertaken by Chiolero et al. examining the prevalence of elevated BP in recent large-scale school-based studies (> 2000 children) published between 1980 and 2006 [2]. This review tabulated studies from the US (Minnesota, Houston, and Delaware), Pakistan, Quebec, Milan, and the Republic of Seychelles using the NHBPEP definition. Most studies in this review documented a high prevalence of systolic HT, with a range of 7.2-19.4% after a single set of measurements. However, only the study done with Houston public school students used data from three separate BP screenings, after which the overall HT prevalence was 4.5% [19]. The study also showed HT in 2.6% of children with normal BMI versus 10.7% among those who were overweight (BMI ≥ 95th percentile). Paradis et al. conducted surveys of Quebec students aged 9, 13, or 16 years, demonstrating increased HT prevalence with each age group (7.0%, 13.0%, and 17% respectively) [5]. In the sample of children from Pakistan published in 2005 [20], the HT prevalence was 15.8% in boys and 8.7% in girls. This is higher than many of the US populations studied despite a substantially lower mean BMI, suggesting that risk factors other than BMI influence BP. For example, it is speculated that the lower average birth weight in Pakistani children may contribute to a higher prevalence of HT [2] given what is known about the inverse association between birth weight and later BP [21].

There have been several large studies done recently in US children that have provided a more accurate estimate of HT prevalence [12, 18-19, 22]. Among them is a cohort study by Hansen et al. [22] on 14,187 children aged 3-18 years in Ohio. This study found a prevalence of 3.6% of children who met the height and age-adjusted criteria for HT after measurement at three or more well care visits, with 3.4% of children having prehypertension. Of those with HT, 3% met criteria for stage 2. Another study [18] assessed the cross-sectional prevalence of HT in 6,790 adolescents in Houston schools between 2003-2005. The BP measurements were performed by oscillometric devices and repeated four times during the initial assessment, then performed on two subsequent occasions for those with persistent BP elevation. Hypertension prevalence was 3.2%, of which 80% was classified as stage 1. The prevalence of prehypertension defined as elevated BP on at least one screening was 15.7%. Only 56% of students with elevated BP fell into the same HT stage after three screenings, demonstrating a significant variability between BP screenings. The prevalence of HT in overweight children has previously been reported to be from around 11% [19]. Similarly this study found that HT and
prehypertension increased with increasing BMI, and occurred in up to 30% of obese students. The classification as overweight was independently associated with HT, with the odds of HT being 4.2-fold higher in overweight students. While the prevalence of HT is best determined in a region-specific manner, it is noteworthy that the US studies demonstrate a high prevalence, given that the expected prevalence that BP will be ≥ 95th percentile after three separate measurements ranges from 1-3% [12].

Few studies have analyzed BP prevalence according to etiology. It is well understood that the likelihood of secondary causes of HT is inversely related to patient age and directly related to degree of BP elevation. In view of the rise in overweight and obesity prevalence however, prevalence studies done at various referral centers indicate that primary HT comprises an increasing proportion of overall HT in the pediatric population [23]. Feld et al. reported in the late 1980s that hypertension in children seen at tertiary care centers was predominantly secondary (84%), and among secondary causes 70% were from renal disease, 15% were from coarctation of the aorta, 7% were renovascular, and 2% were endocrine [24]. A later study from Dallas in the early 1990s showed that among patients referred for HT 77% had secondary causes [25]. In 2001, Flynn reported an apparent shift in the cause of HT among 146 children referred to a pediatric HT clinic over a 5-year period [23, 26]. Nearly 50% of these children had primary HT, of which 40% were overweight and 87% had a positive family history.

Due to the global epidemic of overweight and obesity, the study of HT in children has recently become focused on BP trends. While studies have again shown variable worldwide, recent US data demonstrates an increase in BP levels and the prevalence of HT in children and adolescents since the late 1980s [27-28], although some have emphasized that there has been only a modest increase in BP in contrast to the dramatic rise in overweight and obesity [2]. The data suggest that the rise in BP is only partially accounted for by the rise in overweight, and that other factors have contributed to the increasing prevalence of HT [29]. Din-Dzietham et al. studied national survey data obtained between 1963 and 2002 and applied current definitions of HT in the data analysis. The data demonstrated a decrease in mean BP and prevalence of prehypertension and HT between 1963 and 1988 in children 8-17 years, followed by an upward trend thereafter [28]. More specifically, blacks and Mexican Americans had greater HT prevalence than whites, and the overall increase in prevalence was 2.3% for prehypertension and 1% for HT between 1988 and 1999. This was accounted for in part by the rise in overweight and obesity prevalence, which began 10 years prior to the rise in mean BP levels and HT. It has been suggested that the decrease in prevalence of HT between 1963 and 1988 was not a reliable reflection of the true trend [30]. Rather it signified an increasingly more accurate assessment of BP in children that came with a better understanding of normal BP distribution and appropriate measurement techniques. Data from the National Health and Nutrition Examination Survey (NHANES) was used for cross-sectional studies conducted between 1988-1994 and 1999-2000. These data similarly showed a rise in mean SBP and DBP by 1.4/3.3 mmHg between the two study periods, when adjusted for gender, age, and ethnicity [27]. When adjusted for differences in BMI, the increase was reduced by 29%/12%. Again, the greater rise in mean BP was demonstrated in blacks and Mexican Americans compared with whites.

The rise in mean BP and HT established in US survey data has not been demonstrated globally. A recent school-based survey was done in the island state of Seychelles [10]. This study was conducted annually between 1998 and 2006 among 25,586 children and adolescents aged 4 to 18 years. Obesity prevalence (using Centers for Disease Control criteria) rose on the island by 2.9% and 2.7% for boys and girls, respectively between 1998-2000 and 2004-2006. Mean BMI increased by 0.57 kg/m² and 0.58 kg/m² for boys and girls, respectively. Regardless, BP did not demonstrate a commensurate rise with obesity, and in fact showed a decrease of 3.0/0.4 mmHg in boys and 2.8/0.4 mmHg in girls when adjusted for age and height.

OUTCOMES IN PEDIATRIC HYPERTENSION

As previously mentioned, no studies currently link a specific sustained BP level in children to adverse outcomes in adulthood. However, there are several outcomes of pediatric HT that have been studied, including the tracking of BP from childhood into adulthood and the presence of a multitude of surrogate markers of cardiovascular injury associated with HT [12, 29]. A recent review of 50 cohort studies originating from diverse global populations examined BP tracking, showing significant correlation coefficients between childhood and adult SBP and DBP. The review concluded that the evidence for BP tracking into adulthood was strong, and that the strength of the correlation increased with baseline age [31]. Sun et al. used serial data from 240 men and 253 women in the Fels Longitudinal Study to examine BP tracking [32]. The results showed that HT in adulthood can be predicted in children. Specifically, the odds ratios of HT occurring ≥ 30 years was found to be 3.8 and 4.5 in 5-7 year-old boys and girls who had elevated BP during a single evaluation in childhood, indicating that prevention of adult HT should begin in early childhood. Moreover, the data predict that to remain HT-free in adulthood, childhood BP should remain below the age- and height-adjusted 50th percentile as defined by the NHBPEP [32]. Adding to this data are studies that report increased prevalence of long-term HT in children who have had early successful repair of aortic coarctation [33]. It has been suggested that even brief periods of HT may cause structural changes in resistance vessels, in turn leading to persistent HT [29].

Autopsy studies that have examined tissue from adolescents and young adults with trauma-associated sudden death have shown significant associations between BP
levels or HT and the presence of atherosclerotic lesions in the coronary arteries and aorta [34-35]. Other quantifiable forms of hypertensive target-organ damage are known to occur in children, including left ventricular hypertrophy (LVH) [36], increased carotid artery intimal medial thickness (cIMT) [37-38], retinal arteriolar narrowing [39], and decreased cognitive performance [40-41]. LVH is reported to have prevalences of > 30% in children and adolescents with mild, untreated HT [13]. Recent studies have demonstrated that HT is associated with increased BMI [42], and furthermore that there is no relationship between severity of HT and LVH [43]. These data support recommendations to include echocardiography in the evaluation of hypertensive children as LVH may be discovered regardless of severity. With regard to cognitive function, Lande et al. demonstrated poorer test performance and lower parental rating of executive function in children with elevated BP [40-41].

SUMMARY

Hypertension in children is currently defined according to normative BP data rather than clinical outcomes. The definition varies globally and some large-scale studies have enabled region-specific BP norms to be established. Using the definition from the NHBPEP, several studies have demonstrated an increasing prevalence of pediatric HT associated in part with a rise in overweight and obesity. Others have failed to show increasing trends in BP levels and HT despite increasing obesity prevalence. While the association between BMI and BP is well established, there are other risk factors such as diet, birth weight, and unknown factors which may alter or attenuate the effects of obesity on BP trends [2,29]. The prevalence of prehypertension and HT in U.S. children each have been shown to exceed 3% with a greater than 10% prevalence of HT in obese children and adolescents. With the knowledge that pediatric HT has significant early sequelae and tracks into adulthood, it has become a common and important cause of HT in adults. With the knowledge that HT is associated with increased BMI and HT despite increasing obesity prevalence. While the association between BMI and BP is well established, there are other risk factors such as diet, birth weight, and unknown factors which may alter or attenuate the effects of obesity on BP trends [2,29]. The prevalence of prehypertension and HT in U.S. children each have been shown to exceed 3% with a greater than 10% prevalence of HT in obese children and adolescents. With the knowledge that pediatric HT has significant early sequelae and tracks into adulthood, it has become a common and important cause of both short- and long-term morbidity. Overall, continued study will allow a better understanding of the longitudinal risk associated with various BP percentiles in children and will enable an increasingly more refined definition of pediatric HT from which prevalence can be determined.

REFERENCES