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Autosomal dominant polycystic kidney disease in children

Melissa A. Cadnapaphornchai

Children's Hospital Colorado, University of Colorado Denver, Aurora, Colorado, USA

Abstract

Purpose of review—Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease, affecting one in 500 individuals. The cardinal manifestation of ADPKD is progressive cystic dilatation of renal tubules with kidney enlargement and progression to end-stage renal disease in approximately half of cases by 60 years of age. Although previously considered a condition of adults, it is clear that children and young adults are subject to the complications of ADPKD.

Recent findings—It has been increasingly recognized that interventions early in life are necessary in order to confer the best long-term outcome in this common condition. Therefore, it is imperative for pediatricians to recognize the manifestations and complications of this disease. Until recently ADPKD management focused on general principles of chronic kidney disease. However, several recent clinical trials in children and adults with ADPKD have focused on disease-specific therapies.

Summary—This review will highlight the clinical manifestations, diagnosis, and appropriate management of ADPKD in childhood and will review recent relevant clinical trials in children and adults with this condition.

Keywords

autosomal dominant polycystic kidney disease; management; pediatric

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease, affecting approximately one in 500 individuals worldwide [1]. Although historically termed 'adult' polycystic kidney disease, it is clear that important clinical manifestations including progressive structural kidney disease are evident in childhood and even *in utero* in some cases [2,3]. Cystic kidney disease accounts for nearly 5% of end-stage renal disease (ESRD) in the United States [1]. Early intervention in childhood, which ameliorates the progression of ADPKD to chronic kidney failure, would be anticipated to have major long-term impact on individual health and medical resources. The purpose of this article is to review the clinical findings, diagnosis, and appropriate management of

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Correspondence to Melissa A. Cadnapaphornchai, MD, Kidney Center, Children's Hospital Colorado, 13123 E. 16th Ave, BoxB328, Aurora, CO 80045, USA, Tel: +1 720 777 3932, fax: +1 720 777 7200, Melissa.Cadnapaphornchai@ucdenver.edu.

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ADPKD in childhood and to emphasize the importance of early diagnosis and management of this condition.

Clinical Findings

The cardinal manifestation of ADPKD is bilateral progressive cystic dilation of the renal tubules with eventual compression of normal renal parenchyma, kidney enlargement, and loss of renal function, such that approximately half of affected individuals reach ESRD by 60 years of age [4,5]. Kidney cysts may be evident by prenatal ultrasonography, although more commonly, diffusely enlarged kidneys with variable echogenicity or normal kidneys are observed by current imaging techniques [3,6,7]. Kidney enlargement due to cystic involvement is observed in many affected children, although there is a wide range of severity, even within the same family. ADPKD children demonstrate faster kidney growth by ultrasound than unaffected children, and those with severe kidney enlargement at a young age manifest faster kidney growth than those with mild enlargement or normal kidney size for their age [8]. Children who are diagnosed due to signs or symptoms (e.g., oligohydramnios, hypertension, impaired renal function) before 18 months of age have ‘very early onset’ (VEO) ADPKD and demonstrate larger kidneys with more cysts when adjusted for age than children diagnosed later in life [9]. Such children are at particular risk for hypertension and early loss of kidney function [3].

Structural cystic kidney disease can be associated with acute or chronic flank, back, or abdominal pain in childhood. Such pain has been attributed both to capsular stretch by growing cysts and to cyst hemorrhage, which can occur spontaneously or with minimal trauma. In some cases, recurrent pain is severe, and chronic pain management is required. However, many children are asymptomatic despite evidence of prior cyst hemorrhage on abdominal imaging.

Hypertension affects 10–35% of children with ADPKD [10–13] and is particularly common in VEO ADPKD. The strong correlation between hypertension and larger kidneys has been observed in multiple cohorts of ADPKD children [8,14,15,16^{***}]. Whether hypertension or kidney enlargement is the inciting event is not known but it seems likely that each contributes to the other [17,18]. The presence of hypertension is an ominous sign and is associated with a decrease in estimated glomerular filtration rate (eGFR) over time [15]. Hypertension in an affected parent is associated with increased frequency and earlier age of onset of hypertension in ADPKD offspring [11]. Ambulatory blood pressure monitoring is critical in the assessment of ADPKD children, as nearly one-third of children show exclusively nocturnal hypertension [12,19–22]. The pathogenesis of hypertension in ADPKD is multifactorial and appears to involve the renin–angiotensin–aldosterone, nitric oxide, and sympathetic nervous systems (reviewed in [18]).

Additional renal manifestations of ADPKD in childhood include micro and gross hematuria and proteinuria. Hematuria can occur with cyst hemorrhage, although most cysts are noncommunicating. Overt proteinuria is associated with more advanced structural kidney disease [8,23]. In contrast to adults with ADPKD [23], we have found no correlation

between microalbuminuria and either kidney volume or function in children with ADPKD [15,16^{***}].

As very extensive structural disease is required before any measurable decrease in eGFR, the vast majority of affected children maintain normal eGFR. However, glomerular hyperfiltration is common [24] and portends risk of progression. Glomerular hyperfiltration (24 h urine creatinine clearance ≥ 140 ml/min/1.73m²) is associated with significantly faster decline in eGFR and higher rate of kidney enlargement over time [25]. Because diminished eGFR is a sign of advanced disease, total kidney volume (TKV) has been utilized as an early marker of disease progression [26–28]. TKV measurement by ultrasound correlates well with MRI in most affected children due to their relatively small kidney size compared with affected adults [29].

Urolithiasis affects children with ADPKD at increased frequency compared with the general population, with urine abnormalities similar to those observed in ADPKD adults (e.g., low urine volume, hypocitraturia). Hepatic, pancreatic, and splenic cysts can occur in childhood ADPKD, most commonly in teenagers. However, such cystic involvement rarely constitutes more than a few small cysts. Intracranial aneurysms (ICA) can occur in children with ADPKD [30,31] but are of such rarity that routine screening is not indicated during childhood.

Cardiovascular disease is a major feature of ADPKD. In addition to hypertension, there is increased frequency of cardiac valve abnormalities in both ADPKD children and adults. The prevalence of mitral valve prolapse is 12% in ADPKD children as compared with only 3% in controls [32]. ADPKD children, but not their unaffected siblings, demonstrate a significant correlation between left ventricular mass index (LVMI) and systolic blood pressure [32]. Hypertensive ADPKD children have a significantly higher LVMI than normotensive ADPKD children [15,32]. Interestingly, children with ADPKD and blood pressure in the upper range of normal (75–95th percentile for age, sex, and height) have LVMI similar to that of hypertensive ADPKD children despite significantly smaller TKV[14], suggesting that cardiovascular disease may be an early feature of pediatric ADPKD. Overt left ventricular hypertrophy is uncommon in ADPKD children. Endothelial dysfunction due to disordered nitric oxide and endothelin metabolism occurs in adults with ADPKD [33–35]. Similar studies are ongoing in pediatric ADPKD.

In summary, with the exception of kidney failure and ICA, the clinical manifestations observed in pediatric ADPKD are similar to those seen in affected adults. Attention to these signs and symptoms is therefore indicated during routine follow-up of children with, or at risk of, ADPKD.

Genetics

ADPKD is caused by mutations in two genes: *PKD1* (chromosome 16p13.3), which encodes polycystin-1 (PC1), and *PKD2* (chromosome 4q21), which encodes polycystin-2 (PC2). Although a third gene has been proposed, none has been identified [36]. Among adult patients referred for nephrology evaluation, *PKD1* mutations account for approximately 78% of cases with the remaining 13% of cases due to *PKD2* mutations and 9% due to de-

novo mutations [37–39]. It is estimated, however, that *PKD2* mutations, which typically confer a milder course, may account for up to 25% of mutations in the general population [40]. PC1 is a large integral membrane protein whose structure resembles a receptor or adhesion molecule [41]. PC2 is a six-transmembrane Ca^{2+} -responsive cation channel of the transient receptor potential family [42,43]. PC1 and PC2 are thought to interact via their C-terminal tails with the resulting PC complex playing a role in intracellular Ca^{2+} regulation.

PC1, PC2, and other proteins associated with renal cystic disease have been localized to the primary cilium in the renal tubule and other epithelium. The cilium may function as a flow detector, facilitating calcium influx when flow is present and restricting influx in response to a lack of flow or loss of the PC complex [44]. In this manner, multiple signaling pathways that regulate cell proliferation and fluid secretion, including cyclic adenosine monophosphate (cAMP), are altered in favor of cyst formation [44]. Increasing evidence supports the concept that cysts develop below a specific PC threshold, with the dosage of functional PC correlating with disease severity [45]. Reaching this threshold could be impacted by numerous factors, including the specific somatic mutation; variants in genes including *PKD1*, *PKD2*, and others associated with cystic renal disease; stochastic expression differences between cells; and environmental factors such as kidney injury [46,47]. This concept aligns with the ‘second-hit’ hypothesis of cyst formation [48].

PKD1 is generally associated with more severe disease than *PKD2*, with earlier age at diagnosis, higher number of kidney cysts, earlier onset of hypertension, and faster progression to ESRD [49,50]. The Consortium for the Radiologic Imaging Study of PKD (CRISP) has demonstrated in adults that cysts within *PKD1* and *PKD2* kidneys grow at similar rates; however, kidneys with *PKD1* mutations enlarge faster than *PKD2* kidneys because they contain more cysts [51,52]. Factors associated with early adverse structural and functional outcomes include *PKD1* mutation (particularly truncating mutation), male sex, early onset of hypertension, early and frequent gross hematuria, three or more pregnancies among affected females, and overt proteinuria [53^{***}]. Wide intrafamilial phenotypic variability exists and might further be explained by hypomorphic alleles or modifier genes [54,55,56^{*}].

Diagnosis

Renal ultrasound remains the primary means to diagnose ADPKD in childhood. Such studies are readily obtained, relatively inexpensive, and provide no radiation exposure to the child. The at-risk child (i.e., a parent is known to be affected) can be diagnosed with ADPKD when bilateral kidney cysts are present [57]. A normal ultrasound during childhood does not exclude ADPKD [58]. MRI can detect cysts as small as 2mm [29]; however, such sophisticated imaging is not routinely indicated for clinical diagnosis considering the associated expense and potential need for sedation in young children. It is not uncommon for children with ADPKD to be diagnosed incidentally during imaging obtained for other reasons.

Simple renal cysts are unusual in childhood but do occur. However, the presence of multiple ‘simple’ cysts in the absence of significant chronic medical disease [59] is exceedingly

unusual. When ADPKD is suspected but there is no apparent family history, parents should be screened with ultrasound. The diagnosis of ADPKD in a parent has important implications both for the parent's health and for the risk of inheritance to other offspring.

Prenatal diagnosis of ADPKD is increasing. Sonographic findings are variable and can be difficult to distinguish from other renal cystic disease in the prenatal period. ADPKD can present with enlarged echogenic kidneys with or without discrete cysts. In contrast to autosomal recessive polycystic kidney disease, increased corticomedullary differentiation may be observed. Fetal renal dysfunction with oligohydramnios is unusual in ADPKD and is more commonly observed with bilateral multicystic dysplastic kidneys or autosomal recessive polycystic kidney disease. Parental screening may help elucidate the diagnosis.

Direct mutation analysis (next-generation or Sanger sequencing) is available commercially (~USD \$3000). Consideration must be given to the psychosocial and financial implications of genetic diagnosis, particularly when the proband is asymptomatic. In the United States, the Genetic Information Nondiscrimination Act of 2008 [60] prohibits genetic discrimination in medical insurance and employment but does not address life or disability insurance. It is important for parents to understand these implications, and formal genetic counseling may be indicated. Definitive disease-associated mutations are only found in 40–60% [61], likely due to a sampling phenomenon wherein mutation analysis is only pursued when other clinical data are questionably supportive of the diagnosis. Serial renal ultrasound may prove to be more cost-effective in such situations. In the absence of DNA analysis, the family history of ESRD may be helpful in some cases to predict the mutated gene [62].

Supportive Treatment

For many years, no disease-specific intervention was available for the treatment of ADPKD. Supportive measures were instituted along the general guidelines for chronic kidney disease, with adaptation as appropriate for affected children. Such supportive treatments are reviewed here.

Diet

Dietary intake of salt, protein, and calories is reportedly associated with worsening kidney volume and function in adults with ADPKD involved in the CRISP study [63[■]]; a detailed analysis has not been published. Although dietary protein restriction in an animal model of ADPKD was associated with decreased kidney cyst volume and improved renal function [64], similar effects were not observed in ADPKD adult humans, albeit in the setting of advanced structural and functional disease [65]. Regardless, dietary protein restriction is not advocated in growing children including those with chronic kidney disease [66]; however, excessive protein intake should be avoided with underlying renal disease. To date, no specific diet has been studied in or advocated for children with ADPKD. The Dietary Approaches to Stop Hypertension (DASH) programme encourages a balanced dietary pattern that is rich in fruits, vegetables, and fat-free or low-fat dairy foods and is limited in sodium, sugar-sweetened foods and beverages, red meat, and added fat [67]. It promotes lifelong healthy diet choices and is associated with improved blood pressure, cholesterol concentration, and insulin sensitivity in adolescents with systemic hypertension or diabetes

mellitus in the general population [68–70]. With rising obesity rates in children and the risk for systemic hypertension and other cardiovascular complications in ADPKD, dietary counseling early in life to establish healthy eating patterns with reasonable salt intake makes sense. Other lifestyle interventions targeting healthy body mass index and routine exercise would be anticipated to improve cardiovascular health in general and also potentially support tolerance of the chronic back and flank pain associated with progressive nephromegaly.

High fluid intake

Arginine vasopressin (AVP) is believed to play a critical role in kidney cyst fluid accumulation in ADPKD. Therefore, suppression of AVP could be a key factor to modulate kidney cyst growth in this condition. Results from the TEMPO (Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes) study showed that pharmacologic blockade of AVP with tolvaptan reduced the usual increase in TKV and decline in GFR observed over time in affected adults [71,72]. Suppression of AVP by high fluid intake has also been proposed as therapy for ADPKD. In an animal model of ADPKD, short-term high fluid intake (~3.5 times normal) resulted in urine osmolality below 290 mOsm/kg H₂O with a 30% reduction in the kidney-to-body weight ratio [73]. A 2-week pilot study conducted in eight ADPKD adults demonstrated that a water intake of 2.4–3l/day is sufficient to maintain urine osmolality below 285 mOsm/kg H₂O [74]. Whether this is sufficient to chronically and continuously suppress plasma AVP concentration and associated cyst fluid accumulation is not known [75]. Chronic high fluid intake presents specific difficulties for young children, and any such intervention must be performed under close medical supervision. Certainly high fluid intake may be routinely advised in the setting of PKD-associated urolithiasis.

Avoidance of caffeine

Caffeine-induced inhibition of phosphodiesterase is known to increase the accumulation of cAMP, with subsequent activation of the extracellular signal-related kinase (ERK) pathway to induce cellular proliferation and transepithelial fluid secretion in ADPKD cystic epithelium [76]. This concept has led to the general recommendation to avoid caffeine intake with underlying ADPKD.

Cardiovascular disease surveillance

Due to the increased frequency of valvular abnormalities, children with abnormal cardiac examination or symptoms suggestive of mitral valve prolapse or other cardiac valve disease should be referred for echocardiogram. Periodic echocardiographic assessment may be indicated in children and young adults with ADPKD and hypertension [19].

Other management

ADPKD-associated ICA are rare during childhood (median age at diagnosis 49 years [77]) but are strongly influenced by family history [78]. Based on these findings, we recommend routine screening beginning at 18–21 years of age with a known family history of PKD-associated ICA/hemorrhagic stroke or with no known family history of ADPKD. Even with

such screening, identified ICAs tend to be small and rarely require surgical intervention. Appropriate evaluation is of course indicated with concerning symptoms regardless of the age of the child.

Urolithiasis and urinary tract infection should be evaluated and treated as for children without ADPKD. Chronic back or flank pain may require consultation with a chronic pain team. Avoidance of aspirin and nonsteroidal anti-inflammatory drugs has been empirically recommended in the setting of recurrent cyst hemorrhage. Contact sports may need to be avoided for those children with recurrent cyst hemorrhage or significant nephromegaly. Hyperlipidemia is an unusual finding in ADPKD [79] but should be treated appropriately.

No guidelines exist regarding serial ultrasonography in the routine clinical management of pediatric ADPKD. Certainly repeat imaging is useful when there is concern for rapidly progressive kidney growth, cyst hemorrhage or infection (both better delineated by computed tomography), or other specific clinical concerns. In the absence of systematic measurement of interval kidney growth relative to somatic growth, serial ultrasound may be of limited utility in everyday practice.

Disease-Specific Treatment

In recent years, there have been several clinical trials designed to slow progression of kidney and cardiovascular disease in ADPKD. The mechanisms contributing to cyst formation and fluid accumulation are complex, and it seems likely that antagonism of a combination of such pathways will lead to the most profound impact on cyst growth and preservation of renal function.

Control of hypertension/renin–angiotensin blockade

Blood pressure control is a critical component of all chronic kidney disease management in childhood. The ESCAPE trial found that more aggressive control (blood pressure <50th percentile vs. 50–95th percentile) of chronic hypertension with angiotensin-converting-enzyme inhibition (ACEI) slowed loss of kidney function in children with chronic kidney disease stages 2–4[80]. With a relatively small sample size, we were unable to demonstrate any effect of the degree of blood pressure control with ACEI on either TKV or kidney function in hypertensive children and young adults with ADPKD in a randomized controlled clinical trial [15]. The recently completed double-blind placebo-controlled HALT-PKD clinical trial compared aggressive vs. standard control of blood pressure with either ACEI or combined ACEI and angiotensin-receptor blockade (ARB) in 558 hypertensive ADPKD participants ages 15–49 years with relatively preserved eGFR[81]. Aggressive blood pressure control was associated with a statistically but not clinically significant slowing of the annual percentage increase in TKV over time (5.6 vs. 6.6%, $P = 0.006$) with no differences observed in eGFR between study groups. Combined ACEI/ARB treatment did not alter the rate of increase in TKV or eGFR as compared with ACEI alone. The results of these studies support the conclusion that hypertension in ADPKD signifies advanced disease in childhood.

In contrast, children and young adults with high normal (75–95th percentile) blood pressure represent a target group for intervention with ACEI. Treatment of such children with ACEI to a goal blood pressure below the 50th percentile has been shown to prevent the decline in eGFR and increase in LVMI, which is observed with a blood pressure target at the 90th percentile [15]. Therefore, special consideration should be given to starting ACEI in this group for potential preservation of renal and cardiac function. Blockade of the renin–angioten–sin–aldosterone system with ACEI or ARB remains the preferred treatment for hypertension in pediatric ADPKD. Medication-related hyperkalemia and decreased GFR are rare in pediatric ADPKD [15] as baseline GFR is nearly always normal. The medication risks to the developing fetus should be reviewed as appropriate with patients/families.

Vasopressin V₂ receptor antagonism

Several years ago, Gattone *et al.* [82,83] demonstrated an impressive decrease in kidney cyst fluid accumulation via blockade of the vasopressin V₂ receptor in rat and mouse models of polycystic kidney disease. The multicenter international TEMPO 3:4 study included nearly 1500 adults with ADPKD, eGFR higher than 60 ml/min, and relatively large kidneys (TKV > 750 ml) who were randomized to receive either tolvaptan or placebo for 3 years [71,72]. All participants were advised to avoid thirst by drinking a glass of water after each urination. Participants in the tolvaptan arm demonstrated slower annual increase in TKV than controls (2.8 vs. 5.5%, $P < 0.001$) and slower annual decline in renal function (–2.6 vs. –3.8mg/ml, $P < 0.001$) [71]. Suppression of AVP was observed in both groups, likely due to voluntary increased water intake in placebo participants. In 2013, the US Food & Drug Administration denied the new drug application for tolvaptan as a treatment for ADPKD, citing concern for side effects (including significant liver enzyme elevation in 4.4%) and the high dropout rate (23 vs. 14%). Tolvaptan has not yet been systematically studied in the general pediatric or pediatric PKD populations.

Mammalian target of rapamycin inhibition

The mammalian target of rapamycin (mTOR) pathway plays an important role in cell growth and proliferation, including interaction of the cytoplasmic tail of polycystin 1 with tuberlin [84], and appears to be inappropriately activated in some cystlining epithelial cells in human ADPKD patients and mouse models. Rapamycin, an inhibitor of mTOR, was shown to be effective in reducing cystogenesis in mouse models of ADPKD [84,85]. However, efficacy appears to be dependent on appropriate blood levels [85] and on the tubular origin of cyst development (i.e., effective with proximal tubule but not distal nephron or collecting duct origin) [84,86]. These findings and the observation that human ADPKD transplant recipients treated with mTOR showed a reduction in native polycystic kidney size [84] led to two clinical trials of mTOR inhibitors in ADPKD adults with relatively large kidneys. Sirolimus treatment had no effect on TKV or kidney function; however, dosage was limited due to adverse effects [87]. Everolimus treatment resulted in a slower rate of increase in TKV but a faster decline in eGFR [88] in participants with advanced kidney disease; again there was a high dropout rate (33%). These medications have not been formally studied in pediatric ADPKD. However, the risk–benefit ratio of chronic immunosuppressive therapy with frequent side effects currently restricts the potential for mTOR inhibitor treatment of children with ADPKD.

Statins

In addition to their effect to lower cholesterol, HMG-CoA reductase inhibitors (statins) enhance renal blood flow and GFR and attenuate vascular inflammation through vascular and glomerular nitric oxide production [89]. In an animal model of ADPKD, lovastatin reduced the severity of structural and functional kidney disease [90]. Short-term (4-week) simvastatin treatment of 10 ADPKD adults with normal blood pressure and cholesterol concentration was shown to improve renal blood flow and GFR [91]. Based on these findings, a 3-year randomized double-blind placebo-controlled phase III clinical trial was conducted to assess the effect of pravastatin treatment on kidney and cardiovascular disease progression in children and young adults ages 8–22 years with ADPKD and normal kidney function [79]. The percentage change in height-corrected TKV adjusted for age, sex, and hypertension status over the 3-year period was significantly decreased with pravastatin (23 ± 3 vs. $31 \pm 3\%$, $P = 0.02$) [16^{***}]. The medication was well tolerated with no adverse effects on serum liver or muscle enzymes; no participant discontinued the statin due to side effects. These encouraging results support a role for statins to ameliorate structural kidney disease in young patients with ADPKD. Studies are in progress to examine the potential mechanisms of this effect. Further clinical trials are needed to determine the utility and safety of statins in children under 8 years of age, as the theory remains that the earlier the intervention, the more significant the long-term impact. Potential risks to the fetus with statin exposure should be discussed with patients/families as appropriate.

Screening

Many pediatric nephrologists have advised against routine screening for ADPKD in at-risk children due to the lack of disease-specific treatments for this condition. However, given the recent findings that statins are effective in mitigating progressive structural kidney disease in pediatric ADPKD, and the potential benefits of early ACEI therapy in children as outlined above, it now makes sense that routine screening be offered to children who are potential candidates for such therapies. The potential benefits and risks of screening, including financial and psychosocial implications, need to be discussed with patients/families prior to the institution of routine screening.

Conclusion

Much of what we know about pediatric ADPKD has been extrapolated from adult data. However, studies in affected children are increasing in size and scope. These studies are essential to understand the pathogenesis of this condition. With the frequency of ADPKD in the general population, we will be seeing more and more affected children as screening is widely adopted. Multicenter interventional trials with well tolerated and promising therapies beginning early in life are critical if we are to alter the natural course of this disease.

Acknowledgments

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Key Points

- With the exception of renal insufficiency and intracranial aneurysms, many of the typical findings in adults with ADPKD also affect children with ADPKD. It is important for providers to be aware of these manifestations when caring for children with, or at risk of, ADPKD.
- Further research is needed into the benefits of a balanced low-salt diet and routine exercise, relatively benign interventions, on the management of childhood ADPKD.
- Pravastatin appears to be a well-tolerated and effective agent to slow the progression of structural kidney disease in older children and young adults with ADPKD.
- With the potential therapeutic benefits of angiotensin-converting-enzyme inhibition and statins, we should anticipate more routine screening of at-risk children and therefore increased diagnosis of ADPKD in the pediatric population.