Review of the role of Spironolactone in the therapy of children

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Introduction
At its meeting in October 2007, the WHO Subcommittee of the Expert Committee for the Selection and Use of Essential Medicine considered that the role of Spironolactone should be reviewed in light of potentially newer and more effective medicines for the next meeting. A review of the comparative efficacy, safety, and place in therapy of Spironolactone in children was requested [1].

Background
Spironolactone is a synthetic steroid that competes for the cytoplasmic aldosterone receptor. It increases the secretion of water and sodium, while decreasing the excretion of potassium, by competing for the aldosterone sensitive Na+/K+ channel in the distal tubule of the nephron. Approximately 5% of the filtered Na+ load is ultimately excreted in the urine [2]. Spironolactone effects both gonadal and adrenal steroidogenesis to elevate plasma gonadotrophin levels in children and to act as antiandrogen at the target tissue level [3]. For decades, Spironolactone has been considered as an antagonist at the aldosterone receptors of the epithelial cells of the kidney and was clinically used in the treatment of hyperaldosteronism and occasionally as a potassium-sparing diuretic. Spironolactone may also be useful in the treatment of other conditions such as: portal hypertension, cirrhosis, and left ventricular hypertrophy [4]. Spironolactone not only inhibits production of several cytokines involved in the pathology of many disease, it can also be considered for prolong periods as an economically attractive alternative to modern anti-inflammatory agents [5]. To identify current paediatric guidelines and recommendations for Spironolactone, several resources were reviewed including: WHO publications, paediatric and pharmacology text books, WHO regional databases, FDA website, British National Formulary (BNF), Australian handbook, and international pharmacopoeias. (See table 1).

Table 1: available guidelines for Spironolactone

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<tbody>
<tr>
<td>Paediatric specific guidelines</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Indications</td>
<td>Diuresis in congestive heart failure, ascites, oedema, and nephritic syndrome reduction of hypokalemia induced by other diuretics or amphotericin; primary hyperaldosteronism</td>
<td>Diuresis in congestive heart failure, ascites and oedema, reduction of hypokalemia induced by diuretics or amphotericin</td>
<td>Oedema</td>
<td>Edema, Ascites, Hypertension</td>
</tr>
<tr>
<td>Formulations</td>
<td>Tablet: 25 mg Oral liquid: 1mg/mL,2mg/mL, 5mg/mL</td>
<td>Tablet: 25,50,100 mg Oral suspensions: 5mg/5mL,10mg/5mL, 25mg/5mL, 50 mg/5mL, 100mg/5mL</td>
<td>Tablet: 25mg</td>
<td>U.S.: Tablet:25, 50, 100 mg Canada: Tablet 25, 100 mg</td>
</tr>
<tr>
<td>Dose</td>
<td>Diuresis in congestive heart failure, ascites, oedema and nephrotic syndrome; reduction of</td>
<td>By mouth: Neonate: 1-2 mg/kg daily in 1-2 divided doses; up to 7 mg/kg daily in resistant</td>
<td>Initially 1-3 mg/kg daily in 1-2 divided doses</td>
<td>Initial: oral, 1-3 mg/kg or 30-90 mg/square meter of body surface/day</td>
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</table>
Spironolactone is currently listed in the WHO Model List of Essential Medicines on the complementary list. The administration of Spironolactone can cause side effects such as: fluid and electrolyte imbalance (hyperkalemia, hyponatremia), mild acidosis, and transient elevation of serum urea nitrogen. Hyperkalemia can be fatal and patient's potassium level needs to be checked while on Spironolactone. If hyperkalemia is severe, immediate medical attention is needed including intravenous administration of calcium chloride solution, sodium bicarbonate solution, and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation [6].

**Detailed specification of Spironolactone active pharmaceutical ingredients, dosage forms & strength, publically available formulations, FDA registered formulations**

<table>
<thead>
<tr>
<th>Active ingredient [7]: Spironolactone</th>
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<tbody>
<tr>
<td>Forms and strength available [7]: Tablet; oral: 25 mg, 50 mg, and 100 mg</td>
</tr>
<tr>
<td>Commonly used brand names [8]: Aldactone, Dyrenium, Midamor, Novospiroton</td>
</tr>
</tbody>
</table>

**Pharmacokinetics**

**Absorption / Distribution:** Spironolactone is a steroidal diuretic showing incomplete oral behavior because of its low solubility and slow dissolution rate [9]. Spironolactone is best absorbed if administered with food. The diuretic effect is seen within 48 hours and its half life is about 5 days [10].

**Metabolism / Excretion:** Spironolactone is rapidly and extensively metabolized. The pharmacological activity of Spironolactone metabolites in humans is not known. The metabolites are excreted primarily in the urine and secondarily in bile [6].
**Pharmacodynamics**: Spironolactone is a weak natriuretic agent. It blocks the renin-angiotensin-aldosterone system. It can reduce blood pressure and its maximum hypotensive effects require 3-4 weeks to be fully expressed. It is associated with a dose-related increase in serum potassium levels [11].

**Public Health Burden**

Spironolactone is currently used in the management of several diseases in children including precocious puberty, hypertension, primary aldosteronism, Bartter's syndrome, and Congestive Heart Failure (CHF).

The normal age of pubertal onset is between ages 8-12 for girls and 9-14 for boys. Precocious puberty is the onset of puberty before the age of 8 for girls and 9 for boys. Treatment usually includes medications that can delay further development. Possible complications of precocious puberty include short height and poly cystic ovarian syndrome [12]. Age of pubertal onset has declined significantly in many countries. Changes in age of pubertal onset can have potential influence on adolescent risk taking behavior, such as unprotected sex, substance abuse, and violence, especially in deprived communities contributing to health inequalities [13]. Precocious puberty can be due to several etiologies, gonadotropin dependent or gonadotropin independent [14]. The incidence of precocious puberty is about 0.01-0.05% affecting girls 4-10 more than boys and it is more common among African Americans than Caucasian children [15]. Treatment is usually indicated due to the major psychosocial stress on the affected child [16]. There are two approaches to treat familial male-limited precocious puberty (FMPP). The first is administration of ketoconazole and the second is a combination of Spironolactone and Testolactone [17].

Recent reports from the WHO and the World Bank highlights the importance of chronic diseases such as hypertension as an obstacle to the achievement of good health status [18]. Hypertension is more prevalent in adults, however, in recent years, hypertension and its sequelae are being seen with increasing frequency in children. Hypertension in children is usually secondary to renovascular and renal parenchymal disease and its increased incidence is primarily related to the epidemic of pediatric obesity [19]. Until recently, the incidence of pediatric hypertension has been low, 1-3%, but average blood pressure levels have risen substantially among American children [20]. The incidence of hypertension in infants has risen in recent years for two reasons: better monitoring methods and increasingly successful salvage of smaller newborns [21]. Hypertension can be seen in up to 3% of Neonatal Intensive Care Units (NICU) admissions [22].

Hypertension is among the more prevalent treatable diseases among children and it carries significant short-term and long-term morbidity and mortality [23]. Antihypertensive drugs are indicated in children with symptomatic hypertension, secondary hypertension, established hypertensive target organ damage, stage 2 hypertension, and failure of non pharmacological measures such as weight control, dietary changes, and regular physical activity [24]. Spironolactone has been recommended as part of the antihypertensive drugs for outpatients' management of hypertension in children 1-17 years old. The recommended initial dose is 1 mg/kg/day with a maximum of 3.3 mg/kg/day up to 100 mg/day. All patients treated with diuretics should have their electrolytes monitored shortly after initiating the therapy and periodically thereafter. Spironolactone may cause severe hyperkalemia, especially if given with ACE inhibitors or ARB [25].

Primary aldosteronism is the common cause of secondary hypertension, accounting for approximately 10% of the hypertensive population [26]. Primary aldosteronism is the most
common form of the endocrine hypertension and its early diagnosis and treatment is crucial [27].

Bartter's syndrome is a rare disease characterized by renal potassium wasting. Treatment of Bartter syndrome consists of potassium chloride with one of the following agents: Spironolactone, triamterene, propranolol, and prostaglandin [28].

CHF is associated with high burden of mortality and morbidity, reduced quality of life, and substantial healthcare cost. To reduce the fluid overload, diuretics are considered the first line of treatment. Spironolactone was the only aldosterone antagonist that was recommended for optimal patient management in 2001 European Society of Cardiology guidelines [29]. The most common cause of heart failure in children is volume overload secondary to a left-to-right shunt and the medical therapy is based on diuretics, angiotensin converting enzyme inhibitors, cardiac glycosides, and beta blockers[30]. The main cause of CHF in children in developed countries are: congenital heart defects and cardiomyopathies( 0.34 cases per 100000 of the age-specific population, with 52% occurring in the first year of life[31].

Current paediatric specific guidelines recommend a dose of 1-2g/kg of Spironolactone for the management of several clinical indications in children (see table 2).

Table 2: Indications and dose regimens for Spironolactone in children

<table>
<thead>
<tr>
<th>Indication/s</th>
<th>Dosage</th>
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<tr>
<td>Diuresis in congestive heart failure, ascites, oedema, and nephritic syndrome reduction of hypokalemia induced by other diuretics or amphotericin; primary hyperaldosteronism †</td>
<td></td>
</tr>
</tbody>
</table>
|  | Diuresis in congestive heart failure, ascites, oedema and nephrotic syndrome; reduction of hypokalemia induced by other diuretics or amphotericin.  
**Oral:**  
**Neonate** 1–2 mg/kg daily in 1–2 divided doses.  
**Infant or Child 1 month–12 years** 1–3 mg/kg daily in 1–2 divided doses (maximum 100 mg daily).  
Primary hyperaldosteronism; resistant ascites.  
**Oral:**  
**Neonate** up to a maximum of 7 mg/kg daily may be used.  
**Infant or Child 1 month–12 years** up to a maximum of 9 mg/kg daily (total maximum 400 mg daily) may be used.  
| By mouth:  
Neonate: 1-2 mg/kg daily in 1-2 divided doses; up to 7 mg/kg daily in resistant ascites  
Child 1 month-12 years: 1-3 mg/kg in 1-2 divided doses; up to 9 mg/kg daily in resistant ascites  
Child 12-18 years: 50-100 mg daily in 1-2 divided doses; up to 9 mg/kg daily(max.400 mg daily) in resistant ascites  
† WHO model formulary for children, 2010  
†† BNF for children 2009
Search methods for identification of safety and efficacy data

An online database search for articles published from 1950 to present was conducted using search terms mannitol and children (see appendix 1 for detailed list of search terms). The relevant articles were studied and summarized in combination with other resources, such as National Clearinghouse Guidelines, paediatrics and pharmacology text books, communications with first authors and experts, international pharmacopoeias, and direct communication with FDA. The following databases were searched:

- **Electronic searches**
  1. Cochrane library
  2. Pubmed
  3. Embase
- **Searching other resources:** multiple sources were used wherever possible to validate the data.

**Inclusion criteria:**

- English language articles
- Human subjects
- Types of studies:
  1. Systematic reviews
  2. Randomized controlled trials which subjects were assigned to treatment or control group (placebo-controlled or different drug from Mannitol) on the basis of random allocation.
  3. Reviews
  4. Observational studies
- Types of participant:
  Children between 0-12 years old
- Types of interventions: the treatment group received Mannitol at any dose for any duration at any time

**Exclusion criteria:**

- non English language articles
- animal studies
- Studies not targeting paediatric population
- Studies including paediatric populations, but paediatric specific data not reported separately
- Studies without clear specification of intervention or dose
- Individual case reports

**Results**

See appendix 2 for Cochrane library, Pubmed, and Embase search strategies, number of citations found, and the flow charts for selecting the included articles.
Description of the included studies (see appendix 3 for data extraction tables)

Systematic reviews:
We found only one relevant Cochrane systematic review.

The aim of the review was to assess the risks and benefits of diuretics acting on distal segments of the renal tubule (distal diuretics) in pre-term infants with or developing chronic lung disease (CLD). Of the six studies included in the systematic review, 5 included Spironolactone as part of a treatment arm (4 RCTs and 1 double blind cross over study, total n=141). In each case spironolactone was administered in combination with a thiazide, either hydrochlorothiazide (2mg/kg/12hrs or 3mg/kg/day) or chlorothiazide (20mg/kg/day or 40mg/kg/day). The dose of Spironolactone administered ranged from 1.5 to 4 mg/kg/day. Only 1 RCT (n=33) investigated the effects of administering a thiazide plus spironolactone versus thiazide alone (Hoffman 2000). Overall, the review found that in preterm infants > 3 wks of age with CLD, a 4 week treatment with thiazide and spironolactone improved lung compliance and reduced the need for furosemide. Thiazide and spironolactone decreased the risk of death and tended to decrease the risk for remaining intubated after 8 wks in infants who did not have access to corticosteroids, bronchodilators or aminophylline. However, it found little or no evidence to support any benefit of diuretic administration on need for ventilatory support, length of hospital stay or long-term outcome in patients receiving current therapy. Using spironolactone in addition to thiazide did not significantly affect the risk of needing sodium supplementation (RR 1.48, CI 0.77 to 2.85; RD +0.21, CI -0.12 to +0.54), the risk of needing potassium supplementation (RR 1.21, CI 0.59 to 2.47; RD +0.09, CI -0.25 to +0.43) or the risk of needing either sodium or potassium supplementation (RR 1.29, CI 0.7 to 2.36; RD + 0.15, CI -0.19 to +0.48) (1 RCT, n=33). The use of spironolactone did not affect the change in lung compliance, resistance or tidal volume within 2 weeks. The use of spironolactone did not affect the change in inspiratory oxygen. There is no evidence to support the hypothesis that adding spironolactone to thiazide improves the outcome of preterm infants with CLD.

Original articles (categorized based on therapeutic use of Spironolactone):

Spironolactone use in precocious puberty (see table 4)

Two clinical trials and 1 prospective cohort study investigated the therapeutic use of Spironolactone in children with precocious puberty. Overall, 27 children between the ages of 2.3 and 7.7 years were included in these studies. One of the clinical trials (Laue, 1993, n=8), used Spironolactone (2mg/kg/day in two divided doses, increased to 4mg/kg/day after 2 weeks and then increased again to 5.7 mg/kg/day two weeks later), combined with Testolactone (started as 20 mg/kg/day and increased to 30 mg/kg/day at two weeks and to 40 mg/kg/day at 4 weeks). No specific side effects were reported and the study concluded that the combined therapy is an effective treatment for boys with familial male precocious puberty in whom central activation of the hypothalamic luteinizing hormone releasing hormone (LHRH) neuron has not yet occurred and in whom gonadotropin secretion remains prepubertal. The authors hypothesized that improved preservation of height potential may result from earlier institution of Spironolactone and Testolactone to prevent bone age advancement and from prompt suppression with deslorelin if secondary LHRH dependent precocious puberty should develop.
Another clinical trial (Laue, 1989) divided the 9 subjects into two groups. Group 1 (n=4) received Spironolactone (2 mg/kg/day in two divided doses). After 2 weeks, the dose was increased to 4mg/kg/day and again 2 weeks later, increased to 5.7mg/kg/day. After six months of treatment, Spironolactone was discontinued in two patients and six months later a combination of Spironolactone and Testolactone was initiated. The remaining two patients in this group were initiated on the combination therapy with Spironolactone and Testolactone upon finishing 6 months of monotherapy with Spironolactone. Group 2 (n=5) received Testolactone alone for the initial six months and then Testolactone and Spironolactone for the second 6 months. Dosage was similar to group 1. No abnormalities in electrolytes or in hepatic, renal, or hematologic function were observed during treatment. All 4 patients in group 1 had mild gynecomastia which was resolved either on discontinuation of Spironolactone or upon addition of Testolactone to their therapy. 1/5 in group 2 experienced transient abdominal discomfort which was resolved spontaneously. This study reported that in group 1, growth rate declined from 15.1±3.2 cm/year before treatment to 9.3±1.5 cm/year during Spironolactone and to 6.1±1.3 cm/year during combination therapy with Spironolactone and Testolactone. The rate of bone maturation declined from 2.43±0.14 bone age-year/chronological year before treatment to 2.16±0.17 during Spironolactone therapy and to 0.60±0.23 during combined therapy.

In group 2, growth rate declined from 13.9±1.1 to 6.8±1.9 cm/year during Testolactone therapy and to 5.8±0.8 cm/year during combined therapy with Spironolactone and Testolactone. The rate of bone maturation fell from 2.25±0.26 bone age-year/chronological year to 1.21±0.46 during Testolactone therapy and to 0.78±0.48 during the combined therapy. Overall in group 1 &2, the basal gonadotropin levels did not change significantly after treatment. The peak luteinizing hormone (LH) level after stimulation with LHRH however, increased significantly after combination therapy (29.7±8.5 vs. 4.5±1.0 IU/liter before treatment). The basal plasma testosterone did not change significantly after treatment, except for moderate decline after treatment with Spironolactone alone (13.8±0.9 vs. 8.9±0.5 nmol/L). Testicular volume and pubic hair did not change during treatment with Spironolactone, Testolactone, or both combined. * 6/9 continued to receive the combination therapy for an additional 12 months and maintained normal prepubertal rates of growth and bone maturation. The mean predicted height (± SEM) increased progressively during the combined treatment although the difference between the pre-treatment and post-treatment predictions was not significant (169.5±2.8 at the end of treatment vs. 166.2±4.5 cm before treatment, p=0.29). The authors concluded that blockade of both androgen action and estrogen synthesis with the combination of Spironolactone and Testolactone is an effective short-term treatment for familial precocious puberty.

The Prospective Cohort Study (Leschek, 1999) included 10 children and the intervention included co-administration of Spironolactone and Testolactone and Deslorelin (LHRH analog). Spironolactone was given daily in two oral doses (1.5 mg/kg/day for the first 1-2 weeks and 3.0 mg/kg/day during the second 1-2 weeks and 5.7 mg/kg/day thereafter). Testolactone started at 20 mg/kg/day for the first 1-2 weeks and increased every 1-2 weeks to 30 mg/kg/day and then 40 mg/kg/day. Deslorelin started at the onset of the secondary central precocious puberty at a dose of 4 microgram/kg/day. This study reported that 7/10 had acne improvement and 2/4 boys with aggressive behaviour had improved behavior. However, rarely gastrointestinal upset was noted with Testolactone. This study concluded that long term treatment with Spironolactone, Testolactone, and deslorelin safely normalizes the rate of growth and bone maturation and improves predicted height in boys with FMPP (familial male-limited precocious puberty).
Although no RCT evaluated the therapeutic benefits of Spironolactone in precocious puberty, it seems reasonable to recommend a combination therapy of Spironolactone and Testolactone in children with precocious puberty.

**Spironolactone use in hypertension (See table 5)**

One retrospective study evaluated the therapeutic effect of Spironolactone in 20 children with hyperaldosteronism. Eighteen participants were within our target population (0-12 years) and 16/20 had hypertension. 8/16 was treated with directed monotherapies with spironolactone (12.5 to 100 mg/day), Amiloride (5 to 15 mg), and glucocorticoid suppression (dexamethasone, 0.5 mg, hydrocortisone, 6.25-15 mg/day). This study reported that all 8 treated patients maintained a blood pressure below the 90th percentile. No side effects were reported. This study concluded that compared to the combination of direct therapies, directed monotherapy is often successful in controlling blood pressure in Glucocorticoid-remediable aldosteronism (GRA). Due to the study design, small sample size, and the administration of spironolactone as part of a combination therapy regimen, it is not possible to make a definite conclusion about the use of spironolactone in children with hypertension due to hyperaldosteronism.

**Spironolactone use in hyperaldosteronism (see table 6)**

One Clinical trial investigated the therapeutic effect of Spironolactone in 35 infants between 1 week and 10 months old. 4/15 participants in the study group (n=15) received spironolactone (1-3 mg/kg/24 h. The control group (n=20) received no treatment. No specific benefit or side effect was stated. This study reported that the 4 patients receiving Spironolactone showed improved diuresis and decreased serum aldosterone. Due to the nature of the study and the small sample size, it is not possible to make a definite recommendation.

**Spironolactone use in Bartter syndrome (see table 7)**

One observational study was identified that included 13 children with Bartter's syndrome between the ages of 2 and 32 months investigating the therapeutic effect of Spironolactone. Spironolactone (2 mg/kg/day) was administered if hypokaemia was not corrected despite initial potassium supplement (4 to 8mmol/kg/day). Subsequently, salicylates (10 mg/kg/day) or Indomethacin (3-5 mg/kg/day) was added if hypokalemia was still not corrected. This study reported a significant growth catch-up in 4 patients and increase in serum potassium in 8 patients who received Indomethacin therapy. One patient died of severe pneumonia with respiratory failure from hypokalemic myopathy. Seven patients continued to show growth failure and 3 were hypokalemic in spite of sufficient supplemental potassium therapy. One patient developed renal failure despite the standard therapy. This study concluded that early diagnosis, close follow up, and compliance with treatment may lead to appropriate growth and development of children with Bartter's syndrome. Due to the nature of the study and the small sample size, it is not possible to make a definite recommendation for the inclusion of Spironolactone in children with barter's syndrome.

**Spironolactone use in CHF & congenital heart disease (see table 8)**

One RCT and one case series investigated the therapeutic effect of Spironolactone in 24 children, between the ages of 1-12 years, with CHF and congenital heart disease. In the RCT study, patients were divided into two groups: Group A (n=10) received potassium (1-3 mEq/kg/day) in addition to digoxin (same dose as group B) and chlorothiazide same dose as
group B). Group B (n=11) received Spironolactone (1-2 mg/kg/day every 12 h) in addition to digoxin (0.05 mg/kg/day divided to 3 equal doses followed by maintenance dose of 0.005 mg/kg every 12 h) and chlorothiazide (10-20 mg/kg/day every 12 h). Overall, Group B patients who have continued treatment including Spironolactone were progressing well clinically when seen at follow-up. This study reported that mean daily weight fell for group B but not for group A. Both groups showed significant decrease in hepatomegaly but the decrease was consistently greater in group B after day 2. Significant decrease in respiratory rates began on study day 4 in group B but not until day 6 in group A. There was no significant difference between the numbers of vomiting episodes between the two groups. In group B the 2nd and 3rd mean plasma Na+ values were significantly lower than 1st decreasing from 138.7(±0.78) to 136.1(±0.77) to 134.4(±1.75). There was no significant difference for duration of time in the study; group A (10.1± 1.62) and group B (11.0± 0.83) days. The authors concluded that the addition of Spironolactone hastens and enhances the response to standard treatment with digoxin and chlorothiazide in infants with CHF.

In the Case series study, Spironolactone was administered with various doses (patient 1 received 4mg/kg/day and then increased to 5mg/kg/day, patient 2 received 2.3 mg/kg/day and patient 3 received 1.4 mg/kg/day and then 2.8mg/kg/day). This study reported that patient 1 did not achieve remission of protein loss and normalization of serum protein levels until the addition of Spironolactone to treatment. Authors suggested that a clinical trial of eplerenone, a selective aldosterone inhibitor, in patients with PLE may be the appropriate next step to answer whether the blocking of aldosterone receptors accounts for spironolactone's diuretic effect and whether long-term remission can be achieved. Due to the small sample size for the first study and the nature and small sample size of the second study and the fact that Spironolactone was used in a combination therapy in the RCT study, it is not possible to make a definite conclusion for the beneficial therapeutic effect of Spironolactone in children with CHF or congenital heart disease.

**Spironolactone use in heart disease (see table 9)**

One Prospective study and 1 Retrospective studies evaluated the effect of Spironolactone in patients (overall age range of 10 days- 52 years) with heart disease such as long QT syndrome. The overall number of participants was 28 and 22/28 were within our targeted age range. The Prospective study (Etheridge, 2003) administered Spironolactone (3.5±1.2 mg/kg/day) and KCl (3.3±1.5 mEq/kg/day) for four weeks. This study concluded that long-term oral potassium administration increases serum potassium in patients with long QT syndrome type 2; however no specific conclusion regarding the effectiveness of Spironolactone was made. The retrospective study (Motz, 2005) used Aldactone plus hydrochlorothiazide or furosemide (each 1-2 mg/kg/day) and digoxin. This study concluded that none of the infants, with significant left-to-right shunt, improved while receiving diuretics, Spironolactone, and digoxin alone, but improved after the addition of beta blocker (Propranolol, metoprolol). Due to the nature of the studies, small sample size, and inconclusive data, it is not possible to make a recommendation for inclusion of Spironolactone in therapy of children with heart diseases.

**Spironolactone use in Alport Syndrome (see table 10)**

A clinical study including 5 patients, with the age range of 11-19 years old, with Alport syndrome investigated the effect of 25 mg/day Spironolactone. Only one of the participants was within our target population. It was stated that Spironolactone in addition to angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blocker (ARB) was helpful in
reducing urinary protein excretion. No specific side effect was reported. This study reported that before the start of Spironolactone, U-P/C showed no significant reduction but after the start of Spironolactone, U-P/C was significantly reduced at every time point (p<0.05) and gradually reduced to a minimum (0.13± 0.06 g/g) at 18 months. EGFR remained virtually unchanged throughout the Spironolactone therapy (before Spironolactone treatment: 129.2± 21.4 ml/min and 18 months later 110.1± 30.1 ml/min, p=0.115). Blood pressure dropped 3 months after Spironolactone treatment (systolic BP from 110.8± 5.0 to 91.2 ±6.6 mmHg and diastolic BP from 58.2 ±2.7 to 51.0± 3.0 mmHg). Although serum potassium level was significantly higher 3 months after Spironolactone treatment, none of the patients developed serious hyperkalemia. This study demonstrated that adding Spironolactone to ACEI and ARB may be effective for lowering proteinuria in Alport syndrome. However, a large-scale study with longer follow-up is required to demonstrate whether the results shown in our study translate to improved renal survival for patients with Alport syndrome. Due to the nature of the study and very small sample size, a definite conclusion regarding the inclusion of Spironolactone in the treatment protocol of children with Alport syndrome can not be made.

Spironolactone use in Cystic fibrosis (See table 11)

One observational study including 2 seven months old infants evaluated the therapeutic effect of Spironolactone on the relative changes in electrolyte excretion by the sweat glands and the kidneys in cystic fibrosis. A combination therapy was initiated including: methopyrapone (125mg/4h) and dexamethasone (0.375mg/8h) and Spironolactone (12.5 mg/6h).Duration of this combination therapy was not stated. No specific benefit or side effect is stated. This study reports that similar patterns of increased excretion of Na and Cl and changes in K/Na ratio occurred in urine and sweat, but the magnitude per cent of change in salt excretion and K/Na were greater for renal excretion. Due to the nature of the study and small sample size, it is not possible to make a definite recommendation for the inclusion of Spironolactone in the management of children with cystic fibrosis.

Co-administration of Spironolactone with other diuretics in nephritic syndrome (See table 12)

One prospective cohort study investigated the effect of a combination therapy including furosemide and Spironolactone in 30 children between the ages of 1.4-15 years. 28/30 was within our target age range. The study was done in two phases. Phase one included 10 children and 8/10 were within our target population. Phase two included 20 children, all within our target population. VE ( intravascular volume expansion= fractional excretion of sodium(FeNa)>1%) group received IV furosemide at 1mg/kg/dose(max 40 mg) twice daily and oral Spironolactone at 2.5 mg/kg /dose twice daily(max 100mg twice daily, dose based around 25 mg tablets or its multiples) for sever oedema. VC(intravascular contraction= FeNa<1%) group received IV albumin(25%) at 0.5 g/kg twice daily over 2-3 hours followed by IV furosemide at 1 mg/kg per dose(max 40 mg) at the end of albumin infusion for severe oedema.

One intravascular expansion (VE) patient in phase 2, who only received diuretic, had electrolyte abnormalities and was switched to albumin. This study concluded that there was no difference in hospital stay and weight loss between the VE and intravascular contraction (VC) groups. FeNa is useful in distinguishing VC versus VE in children with nephritic syndrome with severe edema. The use of diuretics alone in VE patients is safe and effective. However, the nature of the study and the small sample size, does not allow a definite
recommendation for the inclusion of Spironolactone in the management of children with nephritic syndrome.

**Spironolactone use in hypertrichosis (see table 13)**

One clinical trial including 12 patients, with mean age 6.9(1.2) years, investigated the effect of Spironolactone in children with hypertrichosis. Spironolactone started at an oral dose of 25 and increased to 100 mg x m (-2) x day8-1) twice daily for one year. No side effects were encountered and Spironolactone therapy was well tolerated and no side effects were observed. This study concluded that Spironolactone may be used safely in the treatment of hypertrichosis. It reduces hair growth to some extent in a number of children, however due to the small sample size; it is not possible to make a recommendation for the use of Spironolactone in children with hypertrichosis.

**Spironolactone use in mineralocortichoid excess (see table 14)**

One case series including 3 children between the ages of 4-9 years with mineralocortichoid excess evaluated the therapeutic effect of Spironolactone. Administration of Spironolactone 100 mg/day orally for 3 days was compared with 3 different protocols: Study 1: ACTH (40 units over 360 min). Study 2: Dietary sodium manipulation (low sodium diet 10 mEq/day, high sodium diet 150 mEq/day, and regular sodium diet 80 mEq/Day). Study 3: Aldosterone (1 mg/day for 3 days) and hydrocortisone (20 mg/day fro 5 days). No specific benefit or side effect was stated. This study reported that Spironolactone administration in patient 1 and 2 resulted in fall of BP to the similar level to that achieved with low sodium diet and significantly lower than that achieved with a regular sodium diet. After 3 days of Spironolactone administration, plasma renin activity (PRA) and 24 hour urinary PH1 aldosterone remained suppressed. Continuous IV hydrocortisone administration caused an increase in blood pressure and decrease in serum potassium demonstrating the abnormal mineralocortichoid activity of cortisol in these patients. Addition of Spironolactone resulted in a decrease in BP, rise in serum potassium, and gradual increase in plasma renin activity. Due to the nature of the study and the very small sample size, it is not possible to make a recommendation for the therapeutic use of Spironolactone in children with mineralocortichoid excess.

**Spironolactone Safety (see table 15)**

One RCT, one clinical trial, one prospective observational study, and one retrospective study evaluated the safety of Spironolactone in children. The RCT (Walker, 1964) included 16 infants between 6-47 days old. 3/16 received a single dose of Spironolactone (50mg) and their urine volume and the urine sodium, potassium, chloride, and creatinine was compared to their urine sample 24 hours before the administration of Spironolactone. No specific benefit or side effect was reported. Three infants who received Spironolactone had a moderately large increase in urine volume and sodium excretion. This study did not make any specific conclusion for Spironolactone.

The clinical trial (Atkinson, 1988) included 30 infants who were divided into 4 groups: 1) Single dose of furosemide (n=6), 2) furosemide plus Spironolactone and hydrochlorothiazide (n=7), 3) Spironolactone (n=12) (2-4 mg/kg/day) and hydrochlorothiazide (1-2 mg/kg/day) for 5 consecutive days (n=29), 4) no diuretic (control). No specific side effect was stated. This study concluded that hypercalciuria was observed in all but the control group. Treatment with any of these diuretics in neonates may be associated with abnormal renal losses of calcium, sodium, chloride, and potassium. Neonates requiring long term treatment with diuretics,
require special consideration, including monitoring of mineral excretion and renal ultrasonography.

The retrospective study (Jenis, 1969) included 15 autopsies of subjects between the ages of 5-75 years who had received 0.025-23.6 grams of Spironolactone. 2/15 was within our target population. Distinctive laminated intracytoplasmic inclusions develop in the human adrenal gland following prolonged Spironolactone therapy. The result of this study suggest a hypothesis: as a consequence of chronic administration of Spironolactone and the sodium diuresis which ensues, there is an activation of the endogenous renin-angiotensin system. Due to the nature of these studies and lack of robust conclusion regarding the safety of Spironolactone in children, it is not possible to make a recommendation for inclusion or exclusion of Spironolactone in the therapy of children.

One article was identified [32] that investigated the age related reference values for the first weeks of life in 34 preterm infants and the possible influence of therapy with dexamethasone(0.1-0.5 mg/kg/day), Spironolactone(3 mg/kg/day), and catecholamines(dopamine 2.5 micrograms/kg/min, dobutamine 7.5 microgram/kg/min). However, because the duration of therapy and the indication for Spironolactone administration were not stated, we did not include it in our safety data table. This study reported that therapy with dexamethasone, Spironolactone or catecholamines showed no influence on creatinine excretion. This study concluded that it might be necessary to lower dosage of renal excreted drugs in very immature and mechanically ventilated infants according to the creatinine clearance.

**Co-administration of Spironolactone with other diuretics in infants with lung disease (See table 16)**

1 double blind cross-over study including 16 infants with bronchopulmonary dysplasia (BPD) investigated the effect of a combination therapy, including Spironolactone with a dose of 1.5 mg/kg/dose twice daily. The patients were divided into two groups: Group 1(n=10) received
successively placebo, theophylline, and theophylline plus diuretics (chlorothiazide 20mg/kg/dose combined with Spironolactone 1.5 mg/kg/dose twice daily). Group 2 (n=9), received theophylline, placebo, and placebo plus diuretics (chlorothiazide 20mg/kg/dose combined with Spironolactone 1.5 mg/kg/dose twice daily) on successive 4-day periods. No specific benefit or side effect was stated, however, this study showed that oral diuretics and theophylline have synergistic effects in infants with BPD (improved airway resistance, dynamic compliance, maximal expiratory flow at functional residual capacity, and time constant at functional residual capacity significantly more than theophylline alone). The authors suggest that combined orally administered diuretics and theophylline are of benefit in some infants with BPD. Due to the small sample size and the nature of the intervention, it is not possible to make a definite recommendation for inclusion of Spironolactone in infants with BPD.

**Discussion:**

Spironolactone has been the drug of choice to treat primary aldosteronism for more than four decades. Serum potassium and creatinine should be monitored frequently during the first 4-6 weeks of therapy, especially in patients with renal insufficiency and diabetes mellitus. Spironolactone increases the half life of digoxin. Spironolactone should not be co-administered with salicylates because salicylates can interfere with the tubular secretion of an active metabolite and decrease the effectiveness of Spironolactone [33].

Treatment of childhood hypertension is difficult for several reasons, lack of extensive scientific data for pharmacokinetics and efficacy of antihypertensive drugs in children, lack of manufactures’ recommendations for the use of antihypertensive agents in children, and a lack of age-appropriate formulation for children. Therefore, the clinical decisions to treat pediatric hypertension relies either on limited data from older studies of agents are no longer considered first line of treatment or to adapt drugs studied in adults for pediatric use[34].

Although no specific study investigated the side effects of Spironolactone in children comprehensively, because Spironolactone is a non-selective aldosterone receptor antagonist, endocrine-related adverse effects, such as gynecomastia, are relatively common with this medicine. The selective aldosterone receptor antagonist eplerenone is associated with fewer endocrine-related side effects [2]. The side effects of Spironolactone are related to its antagonistic action against the testosterone receptor; it causes gynecomastia, mastalgia, impotence, and menstrual irregularities [35]. Spironolactone side effects include: potassium retention, GI irritation, rash, gynecomastia, hyperchloremic metabolic acidosis, amenorrhea, anorexia, agranulocytosis, hyponatremia. It is contraindicated in renal failure and should be used with caution if CI Cr<10 ml/min. Drug interactions include. Hyperkalemia when used with other potassium sparing drugs; may decrease hypoprothrombinemia effects of anticoagulants [36].

Potassium sparing diuretics can alter digoxin pharmacokinetics [37]. Spironolactone is one of the drugs have been shown to interact with digoxin when co-administered; however, most of data available is derived from the adult patients. Due to the difference in pharmacokinetic and Pharmacodynamics between children and adults, a direct extrapolation of adult population to the pediatric population is not permitted [38]. Spironolactone can also interact with ACE inhibitors (can cause hyperkalemia) and potassium supplements [39]. Eplerenone is a new selective aldosterone receptor antagonist that has been approved for patients with left ventricular dysfunction and clinical evidence of heart failure following acute myocardial infarction. Compared to Spironolactone, it has greater selectivity for aldosterone receptors than for steroid receptors, and has superior pharmacokinetic properties [40]. Spironolactone and eplerenone have similar potencies and mineralocorticoid effects but
Eplerenone may have fewer endocrine disturbances due to its lower binding affinity for progesterone and androgen receptors [41].

Spironolactone has been the subject of a large RCT in adult population and Randomized Aldactone Evaluation Study (RALES), by Pitt et al in 1999, was the first trial (RCT) that showed the beneficial effect Spironolactone in adult patients with CHF. 822/1663 patients received Spironolactone (25 mg daily) and 841 received placebo. The treatment group showed a 30% decrease in death [42].

Eplerenone has also been the subject of a RCT and Eplerenone post-Acute Myocardial Infarction heart failure Efficacy and Survival Study (EPHESUS), by Pitt et al in 2003, investigated the effects of eplerenone against placebo in adult patients with myocardial infarction complicated by left ventricular dysfunction. Compare to placebo, the relative risk of death from any cause was 0.85 in eplerenone group and the relative risk of death or hospitalization for cardiovascular events was 0.87. The reduction in the risk of sudden death from cardiac causes was statistically significant [43].

List of clinical trials, listed on ClinicalTrial.gov, including the use of Spironolactone in children:

Four clinical trials were listed as completed [44]:

1) "Treatment of boys with precocious puberty" (NCT00001202). Sponsored by Eunice Kennedy Shriver national Institute of Child health and Human Development (NICHD) and included boys ≤ 10 years with familial male precocious puberty treated with Spironolactone, Testolactone, and Desrolerin. The estimated study completion date was recorded as January 2004; however, we could not find any published data for this trial.

2) "Effects of Spironolactone on insulin resistance in patients with chronic heart failure" (NCT00664222). Sponsored by the Tottori University Hospital and included patients with CHF (age was not specified) treated with Spironolactone (25 mg/day) plus furosemide (20 mg/day) for 16 weeks. This trial was listed as completed; however, we could not find any published data for this clinical trial.

3) Effects of Spironolactone on circulating Matrix Metalloproteinases (MMPs) in patients with chronic heart failure" (NCT00663195). Sponsored by the Tottori University Hospital and included patients with CHF (age was not specified) treated with Spironolactone (25 mg/day) plus furosemide (20 mg/day) for 16 weeks. This trial was listed as completed; however, we could not find any published data for this clinical trial.

4) "Spironolactone combined with captopril and carvedilol for the treatment of patients with pulmonary arterial hypertension associated with congenital heart disease-focus on pulmonary artery" (NCT00240656). Sponsored by Hebei medical University, China. The age of the participants was not stated and although listed as completed, we could not find any published data for this trial.
Conclusion:  
Spironolactone is currently used in the management of several diseases including precocious puberty, hypertension, primary aldosteronism, Bartter's syndrome, and CHF. There is a lack of comprehensive studies evaluating the therapeutic effects of Spironolactone in children. We only identified one systematic review assessing the risks and benefits of diuretics acting on the distal segments of the renal tubule in preterm infants with or developing chronic lung disease. This systematic review concluded that preterm infants older than 3 weeks of age with chronic lung disease, acute and chronic administration of distal diuretics improve pulmonary mechanics, however, spironolactone was not administered alone, sample size was small, and the overall findings were not conclusive.

Precocious puberty is a clinical situation that dictates major psychosocial stress on the affected child and the parents. Therefore, although no RCT evaluated the therapeutic benefits of Spironolactone in precocious puberty, it seems reasonable to recommend a combination therapy of spironolactone and testolactone in children with precocious puberty. In most studies that were identified, spironolactone was used as part of a combination therapy. Moreover, the majority of the identified studies are of different designs, such as retrospective, prospective, observational studies, and case series which makes it difficult to come into a definite conclusion about spironolactone's place in the therapy of children with different diseases such as hypertension, primary aldosteronism, Bartter's syndrome, Alport syndrome, CHF and congenital heart diseases, mineralocorticoid excess, hypertrichosis, nephritic syndrome, BPD, and cystic fibrosis.

Eplerenone is a new selective aldosterone receptor antagonist that has been approved for heart failure. Although both Spironolactone and eplerenone have been evaluated for their efficacy, no studies have directly compared these two drugs [45]. Therefore, it is not clear if Eplerenone could be recommended for children. Overall there is a lack of pediatric specific safety and efficacy data for spironolactone and adult related data is used to implement guidelines for the use of spironolactone in children.
References:

6) Facts & Comparisons.com
7) Drugs @FDA
8) Drugs.com
12) Mayoclinic.com


32) Sonntag J., Prankel b. and Waltz, S. Serum creatinine concentration, urinary creatinine excretion and creatinine clearance during the first 9 weeks in preterm infants with a birth weight below 1500 g. European journal of pediatrics 1996 155:9(815-819)


37) Marcus FI. Pharmacokinetic interactions between digoxin and other drugs. J Am Coll Cardiol. 1985 May;5(5 Suppl A):82A-90A


44) ClinicalTrial.gov

Appendix 1: Search terms

Pubmed


2. "Spironolactone"[Mesh]

Embase

1. "Spironolactone"[Mesh]

2. 'child'/exp OR 'child' OR 'children'/exp OR 'children' OR 'youth'/exp OR 'youth' OR youth* OR newborn* OR 'newborn'/exp OR 'newborn' OR 'new born' OR 'childhood disease'/exp OR 'childhood disease' OR 'baby'/exp OR 'baby' OR babies OR 'infant'/exp OR 'infant' OR infant* OR childhood* OR toddler* OR kid OR kids OR 'young patient' OR boy* OR girl* OR 'young age' OR paediatr* OR paediatr* OR 'child death'/exp OR 'child death' OR 'child health'/exp OR 'child health' OR 'child care'/exp OR 'child care' OR 'childhood mortality'/exp OR 'childhood mortality' OR 'child hospitalization'/exp OR 'child hospitalization' OR 'pediatric hospital'/exp OR 'pediatric hospital' OR child*

3. 'review'/exp OR 'review' OR 'medline'/exp OR medline OR 'medlars'/exp OR medlars OR 'pubmed'/exp OR pubmed OR 'scisearch'/exp OR scisearch OR 'psychlit'/exp OR psychlit OR 'psychlit'/exp OR psychlit OR 'psychinfo'/exp OR psychinfo OR 'electronic database' OR hand NEAR/5 search* OR manual* NEAR/5 search* OR bibliographic NEAR/5 database* OR pooled NEAR/5 analys* OR pooling OR peto OR sesimonian OR fixed NEAR/5 effect OR 'mantel haenszel' OR 'meta analysis'/exp OR 'meta analysis' OR 'retracted article'/exp OR 'retracted article' OR systematic* NEAR/5 review* OR systematic* NEAR/5 overview* OR quantitative* NEAR/5 review* OR quantitative* NEAR/5 overview* OR methodologic* NEAR/5 review* OR methodologic* NEAR/5 overview* OR integrative NEAR/5 review* OR research NEAR/5 integration OR quantitative* NEAR/5 synthesis* OR embase:ti

Pubmed Systematic review search

Search term: "Spironolactone"[MeSH] AND systematic [sb]
Appendix 2: Search strategies

**Pubmed**


Results: 1866521

2) Search "Spironolactone"[Mesh] Results: 4891

3) Search #1 AND #2 Results: 216

**Pubmed Systematic Review**

1) Search "Spironolactone"[MeSH] AND systematic [sb]

2) Results: 32

**Embase**

1) Search 'spironolactone'/exp OR 'spironolactone'

Results: 19,685

2) Search 'child'/exp OR 'child' OR 'children'/exp OR 'children' OR 'youth'/exp OR 'youth' OR youth* OR newborn* OR 'newborn'/exp OR 'newborn' OR 'new born' OR 'childhood disease'/exp OR 'childhood disease' OR 'baby'/exp OR 'baby' OR babies OR 'infant'/exp OR 'infant' OR infant* OR childhood* OR 'toddler'* OR kid OR kids OR 'young patient' OR boy* OR girl* OR 'young age' OR pediatric* OR paediatric* OR 'child death'/exp OR 'child death' OR 'child health'/exp OR 'child health' OR 'child care'/exp OR 'child care' OR 'childhood mortality'/exp OR 'childhood mortality' OR 'child hospitalization'/exp OR 'child hospitalization' OR 'pediatric hospital'/exp OR 'pediatric hospital' OR child*

Results: 3,192,056

3) Search 'review'/exp OR 'review' OR 'medline' OR 'medline'/exp OR medline OR 'medlars' OR 'medlars'/exp OR medlars OR 'pubmed' OR 'pubmed'/exp OR pubmed OR 'scisearch'/exp OR scisearch OR 'psychlit'/ OR 'psychlit'/exp OR psychlit OR 'psyclit'/exp OR psyclit OR 'psychinfo'/exp OR psychinfo OR 'electronic databases' OR 'electronic database' OR hand NEAR/5 search* OR manual* NEAR/5 search* OR bibliographic NEAR/5 database* OR pooled NEAR/5 analys* OR pooling OR peto OR sesimian OR fixed NEAR/5 effect OR 'mantel haenszel' OR 'meta analysis'/exp OR 'meta analysis' OR 'retracted article'/exp OR 'retracted article' OR systematic* NEAR/5 review* OR systematic* NEAR/5 overview* OR quantitative* NEAR/5 review* OR quantitative* NEAR/5 overview* OR methodologic* NEAR/5 review* OR methodologic* NEAR/5 overview* OR integrative NEAR/5 review* OR research NEAR/5 integration OR quantitative* NEAR/5 synthesis* OR embasci

Results: 18,041,264

4) Search #1 AND #2 AND #3

Results: 2,264
### Appendix 3: Data Extraction Tables

**Table 3: Brion, 2002, Cochrane Systematic review**
Clinical question: to assess the risks and benefits of diuretics acting on distal segments of the renal tubule in preterm infants with or developing chronic lung disease. Total number of studies included in review: 6
Studies including Spironolactone: 4 RCTs (total n=131), 1 double blind cross over study (n=10)

<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffman, 2000 Pennsylvania Hospital, USA</td>
<td>Double-blind randomized placebo-controlled trial</td>
<td>26-36 weeks</td>
<td>33</td>
<td>Study group (n=17) received Spironolactone (1.5 mg/kg per dose orally twice daily) and chlorothiazide (20 mg/kg per dose orally twice daily)</td>
<td>Control group (n=16) received the same dose of chlorothiazide and a placebo</td>
<td>Pulmonary mechanics, electrolyte balance, and the need for sodium or potassium supplementation</td>
<td>None stated</td>
<td>None stated</td>
<td>The use of Spironolactone did not affect the change in lung compliance, resistance or tidal volume within 2 weeks. The use of Spironolactone did not affect the change in inspiratory oxygen Using Spironolactone in addition to thiazide did not significantly affect the risk of needing sodium supplementation (RR 1.48, CI 0.77 to 2.85; RD +0.21, CI -0.12 to +0.54), the risk of needing potassium supplementation (RR 1.21, CI 0.59 to 2.47; RD +0.09, CI -0.25 to +0.43) or the risk of needing either sodium or potassium supplementation (RR 1.29, CI 0.7 to 2.36; RD + 0.15, CI -0.19 to +0.48)</td>
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<tr>
<td>Kao, 1994 Intensive care nursery, Children's Hospital, Oakland, California</td>
<td>Double-blind randomized placebo-controlled trial</td>
<td>Infants (11.1±4.0 - 12.1±3.9 weeks)</td>
<td>49 (43 completed the study)</td>
<td>Diuretic group (n=22) received chlorothiazide (40 mg/kg) and Spironolactone (4 mg/kg per day) **3/22 infants with evidence of pulmonary edema, respiratory distress, or excessive weight gain received furosemide (1 mg/kg IV or 2mg/kg orally)</td>
<td>Placebo group (n=21) * 9/21 infants with evidence of pulmonary edema, respiratory distress, or excessive weight gain received furosemide (1 mg/kg IV or 2mg/kg orally)</td>
<td>To determine whether patients benefit from continuing diuretic administration until they no longer require oxygen. Secondary outcomes: natural history of BPD, by measuring pulmonary mechanics during 1st year of life</td>
<td>The respiratory score improved significantly in the diuretic group</td>
<td>None stated</td>
<td>Chronic diuretic therapy significantly improved lung compliance at 4 wks (WMD 0.62ml/cm H2O/kg, CI 0.38 to 0.86, n=43) and at 20 wks (WMD 0.25ml/cm H2O/kg, CI 0.02 to 0.48) Long-term diuretic therapy in stable infants with oxygen-dependent bronchopulmonary dysplasia, after extubation, improves their pulmonary function and decrease their functional inspired oxygen requirements, but does not decrease the number of days that they require supplemental oxygen. The improvement in pulmonary function associated with diuretic therapy is not maintained after treatment is discontinued.</td>
</tr>
<tr>
<td>Citation &amp; Date</td>
<td>Study Design</td>
<td>Age range</td>
<td># of patients</td>
<td>Intervention &amp; Dose</td>
<td>Comparison</td>
<td>Outcomes</td>
<td>Benefits</td>
<td>Side effects</td>
<td>Results/Comments</td>
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<td>Engelhardt 1989,</td>
<td>Randomized placebo-controlled trial but was not blinded</td>
<td>Infants(7.8 ±2.1 - 8.8± 4.2 weeks)</td>
<td>21</td>
<td>Treatment group(n=12) received a 1:1 mixture of hydrochlorothiazide and Spironolactone(3 mg/kg/day of both compounds) for 1 week</td>
<td>Control group (n=9) received no treatment</td>
<td>Dynamic lung compliance, total pulmonary resistance, and haemoglobin oxygen saturation were measured the first and last day of each study period</td>
<td>No beneficial effect of Spironolactone/hydrochlorothiazide combination on lung function was detected</td>
<td>None stated</td>
<td>Although co-administration of hydrochlorothiazide and Spironolactone significantly increased urine output, neither lung mechanics nor oxygenation was improved by the intervention.</td>
</tr>
<tr>
<td>Albersheim, 1989, British Columbia's Children Hospital, Canada</td>
<td>Randomized double-blind control trial</td>
<td>Premature infants(36.5± 4.7-40.5± 9.0 days)</td>
<td>35</td>
<td>Treatment group(n=19) received hydrochlorothiazide(2 mg/kg every 12 hours) and Spironolactone(1.5 mg/kg every 12 hours enterally) for 8 weeks</td>
<td>Placebo group(n=15) received equal volume of the drug vehicle for 8 weeks</td>
<td>Survival at discharge. Secondary outcomes: total no. of ventilator days; hospital days; pulmonary function; O2 requirement; no. of doses of furosemide needed clinically</td>
<td>None stated</td>
<td>None stated</td>
<td>There was a significant difference in the proportion of infants discharged alive between the treatment group (84%) and the placebo group (47%). All deaths in this study were a consequence chronic respiratory failure Long term diuretic therapy improves outcome in infants with bronchopulmonary dysplasia (BPD). Hydrochlorothiazide and Spironolactone therapy in infants with BPD resulted in improved total respiratory system compliance over time, with decreased lung damage and increased survival rate.</td>
</tr>
<tr>
<td>Kao, 1984</td>
<td>Cross-over design</td>
<td>Preterm infants (gestational age: 29.0±3.2 weeks)</td>
<td>10</td>
<td>2)Thiazide(40 mg/kg/day q12h) and Spironolactone(3 mg/kg/day q12h) for one week followed by one week placebo(n=5)</td>
<td>2) vice versa (n=5)</td>
<td>2) pulmonary mechanics</td>
<td>2) Patients did not require oxygen. Baseline pulmonary values were similar between both groups</td>
<td>None stated</td>
<td>Patients did not require oxygen. Baseline values were similar between patients initially started on placebo and those started on diuretics</td>
</tr>
</tbody>
</table>
Table 4: Spironolactone use in precocious puberty

<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laue, 1993 NIH, USA</td>
<td>Clinical trial</td>
<td>2.4-7.6 years</td>
<td>8</td>
<td>Spironolactone + Testolactone Dose: Spironolactone (2mg/kg/day in two divided doses and increased to 4mg/kg/day after 2 weeks and again increased to 5.7 mg/kg/day two weeks later). Testolactone (started as 20 mg/kg/day and increased to 30 mg/kg/day at two weeks and to 40 mg/kg/day at 4 weeks)</td>
<td>None</td>
<td>Rates of growth and bone maturation (height, testicular volume, pubic hair stage) and hormone measurements (estradiol, testosterone, LH, FSH, gonadotropins)</td>
<td>None stated</td>
<td>None was reported</td>
<td>The authors conclude that this combined therapy is effective treatment for boys with familial male precocious puberty in whom central activation of the hypothalamic LHRH neuron has not yet occurred and in whom gonadotropin secretion remains prepubertal. The authors hypothesize that improved preservation of height potential may result from earlier institution of Spironolactone and Testolactone to prevent bone age advancement and from prompt suppression with deslorelin if secondary LHRH dependent precocious puberty should develop.</td>
</tr>
<tr>
<td>Laue, 1989 The Clinical Center at NIH, USA</td>
<td>Clinical trial</td>
<td>3.3-7.7 years</td>
<td>9</td>
<td>Group 1(4/9): Spironolactone (2 mg/kg/day in two divided doses). After 2 weeks, the dose was increased to 4mg/kg/day and again 2 weeks later, increased to 5.7mg/kg/day. After six months of treatment, Spironolactone was discontinued in two patients and six months later a combination of Spironolactone and Group 2(5/9): Testolactone alone for the initial six months and then Testolactone and Spironolactone for the second 6 months. Dosage was</td>
<td>Rates of growth and bone maturation, levels of gonadotropin and sex steroids, testicular volume and pubic hair</td>
<td>No abnormalities in electrolytes or in hepatic, renal, or hematologic function were observed during treatment</td>
<td>All 4 patients in group 1 had mild gynecomastia which was resolved either on discontinuation of Spironolactone or</td>
<td>Group 1: growth rate declined from 15.1±3.2 cm/year before treatment to 9.3±1.5 cm/year during Spironolactone and to 6.1±1.3 cm/year during combination therapy with Spironolactone and Testolactone. The rate of bone maturation declined from 2.43±0.14 bone age-year/chronological year before treatment to</td>
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<tr>
<td>Citation &amp; Date</td>
<td>Study Design</td>
<td>Age range</td>
<td># of patients</td>
<td>Intervention &amp; Dose</td>
<td>Comparison</td>
<td>Outcomes considered</td>
<td>Benefits</td>
<td>Side effects</td>
<td>Results/Comments</td>
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<td>Testolactone was initiated. The remaining two patients in this group were initiated on the combination therapy with Spironolactone and Testolactone upon finishing 6 months of monotherapy with Spironolactone.</td>
<td>similar to group 1.</td>
<td></td>
<td>treatment.</td>
<td>upon addition of Testolactone to their therapy. 1/5 in group 2 experienced transient abdominal discomfort which was resolved spontaneously.</td>
<td>2.16±0.17 during Spironolactone therapy and to 0.60±0.23 during combined therapy. Group 2: growth rate declined from 13.9±1.1 to 6.8±1.9 cm/year during Testolactone therapy and to 5.8±0.8 cm/year during combined therapy with Spironolactone and Testolactone. The rate of bone maturation fell from 2.25±0.26 bone age-year/chronological year to 1.21±0.46 during Testolactone therapy and to 0.78±0.48 during the combined therapy. Group 1 &amp; 2: the basal gonadotropin levels did not change significantly after treatment. The peak LH level after stimulation with LHRH however, increased significantly after combination therapy (29.7±8.5 vs. 4.5±1.0 IU/liter before treatment). The basal plasma testosterone did not change significantly after treatment, except for moderate decline after treatment with Spironolactone alone (13.8±0.9 vs. 8.9±0.5 nmol/L). Testicular volume and pubic hair did not change during treatment.</td>
</tr>
<tr>
<td>Citation &amp; Date</td>
<td>Study Design</td>
<td>Age range</td>
<td># of patients</td>
<td>Intervention &amp; Dose</td>
<td>Comparison</td>
<td>Outcomes considered</td>
<td>Benefits</td>
<td>Side effects</td>
<td>Results/Comments</td>
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</tr>
<tr>
<td>Leschek, 1999, NIH, USA</td>
<td>Prospective Cohort Study</td>
<td>2.3-5.6 years</td>
<td>10</td>
<td>Co-administration of Spironolactone and Testolactone and Deslorelin (LHRH analog). Spironolactone was given daily in two oral doses (1.5 mg/kg/day fro the first 1-2 weeks and 3.0 mg/kg/day during the second 1-2 weeks</td>
<td>None stated</td>
<td>Growth rate, rate of bone maturation, predicted height</td>
<td>7/10 had acne improvement and 2/4 boys with aggressive behaviour</td>
<td>Rarely gastrointestinal upset was noted with Testolactone</td>
<td>Long term treatment with Spironolactone, Testolactone, and deslorelin safely normalizes the rate of growth and bone maturation and improves predicted height in boys with FMPP (familial male-limited precocious puberty)</td>
</tr>
</tbody>
</table>

with Spironolactone, Testolactone, or both combined.
* 6/9 continued to receive the combination therapy for an additional 12 months and maintained normal prepubertal rates of growth and bone maturation. The mean predicted height (± SEM) increased progressively during the combined treatment although the difference between the pre-treatment and post-treatment predictions was not significant (169.5±2.8 cm at the end of treatment vs. 166.2±4.5 cm before treatment, p=0.29).
The authors concluded that blockade of both androgen action and estrogen synthesis with the combination of Spironolactone and Testolactone is an effective short-term treatment for familial precocious puberty.
Table 5: Spironolactone use in hypertension

<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulby, 2001, International registry for Glucocorticoid-remediable aldosteronism(GRA)</td>
<td>Retrospective study</td>
<td>1 month-18 years</td>
<td>18/20 within our age range 16/20 had hypertension</td>
<td>8/16 were treated with directed monotherapies with Spironolactone(12.5-100 mg/day), Amiloride(5-15 mg), and glucocorticoid suppression( dexamethasone, 0.5 mg, hydrocortisone, 6.25-15 mg/day)</td>
<td>Combination of directed therapies</td>
<td>Blood pressure</td>
<td>All 8 treated patients maintained a blood pressure below the 90th percentile</td>
<td>None stated</td>
<td>Directed monotherapy is often successful in controlling blood pressure in GRA.</td>
</tr>
</tbody>
</table>
### Table 6: Spironolactone use in hyperaldosteronism

<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baylen, 1980 Children's Hospital medical Center, Cincinnati,</td>
<td>Clinical trial</td>
<td>Study group: 1 week -10 months</td>
<td>Study group(n=15)</td>
<td>4/15 received spironolactone 81-3 mg/kg/24 h</td>
<td>No treatment</td>
<td>Body weight, serum osmolality, urine volume and sodium to potassium concentration ratio, and serum aldosterone and renin</td>
<td>None stated</td>
<td>None stated</td>
<td>In 4 patients receiving Spironolactone, resulted in improved diuresis and decreased serum aldosterone. The authors conclude that because they observed hyperaldosteronism in infants with a variety of congenital and acquired cardiac lesions, it is an important factor in fluid and salt retention in infants with heart failure and occurrence of hyperaldosteronism should be considered in the management of infants with such failure and signs of fluid retention refractory to treatment.</td>
</tr>
</tbody>
</table>
Table 7: Spironolactone use in Bartter syndrome

<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yaser Khalil, 2002 Al-Adan, Mubarak Al-Kabeer, Al-Jahra Hospitals, Kuwait</td>
<td>Observational study?</td>
<td>2-32 months</td>
<td>13</td>
<td>Initial potassium supplement (4-8mmol/kg/day) followed by spironolactone (2 mg/kg/day) if hypokalemia was not corrected. Subsequently, salicylates(10 mg/kg/day) or Indomethacin(3-5 mg/kg/day) was added if hypokalemia was still not corrected</td>
<td>Not stated</td>
<td>Growth catch-up (weight and height), serum potassium level.</td>
<td>Significant growth catch-up in 4 patients and increase in serum potassium in 8 patients who received indomethacin therapy.</td>
<td>One patient dies of severe pneumonia with respiratory failure from hypokalemic myopathy. Seven patients continued to show growth failure and 3 were hypokalemic in spite of sufficient supplemental potassium therapy. One patient developed renal failure despite the standard therapy.</td>
<td>Early diagnosis, close follow up, and compliance with treatment may lead to appropriate growth and development of children with Bartter’s syndrome</td>
</tr>
<tr>
<td>Citation &amp; Date</td>
<td>Study Design</td>
<td>Age range</td>
<td># of patients</td>
<td>Intervention &amp; Dose</td>
<td>Comparison</td>
<td>Outcomes considered</td>
<td>Benefits</td>
<td>Side effects</td>
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</table>
| Hobbins. 1981, Cardiology ward, Hospital for Sick Children, Canada | Randomized control trial | 1-12 months | 21 | Group B(n=11) received Spironolactone( 1-2 mg/kg/day every 12 h) in addition to digoxin(0.05 mg/kg/day divided to 3 equal doses followed by maintenance dose of 0.005 mg/kg every 12 h) and chlorothiazide(10-20 mg/kg/day every 12 h) | Group A(n=10) received potassium(1-3 mEq/kg/day) in addition to digoxin(same dose as group B) and chlorothiazide same dose as group B) | Clinical progress: Daily clinical observation of vital signs, weight, hepatomegaly, and vomiting. | Group B patients who have continued treatment including Spironolactone were progressing well clinically when seen at follow-up | 5/10 in group A and 3/11 in group B vomited within one hour of ingestion of medications. Electrocardiogram and clinical assessment indicated no adverse effect of treatment in either group. | Mean daily weight fell for group B but not for group A. Both groups showed significant decrease in hepatomegaly but the decrease was consistently greater in group B after day 2. Significant decrease in respiratory rates began on study day 4 in group B but not until day 6 in group A. There was no significant difference between the numbers of vomiting episodes between the two groups. In group B the 2nd and 3rd mean plasma Na+ values were significantly lower than 1st decreasing from 138.7(±0.78) to 136.1(±0.77) to 134.4(±1.75). There was no significant difference for duration of time in the study; group A
<table>
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<tr>
<th>Citation &amp; Date</th>
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<th># of patients</th>
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<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringel, 2003 Johns Hopkins Hospital, USA</td>
<td>Case series</td>
<td>1-10 years</td>
<td>3</td>
<td>Spironolactone , various doses( patient 1 received 4mg/kg/day and then increased to 5mg/kg/day, patient 2 received 2.3 mg/kg/day and patient 3 received 1.4 mg/kg/7day and then 2.8mg/kg/day)</td>
<td>None</td>
<td>Duration of remission of protein losing enteropathy</td>
<td>Patient 1 did not achieve remission of protein loss and normalization of serum protein levels until the addition of Spironolactone to treatment</td>
<td>None stated</td>
<td>(10.1± 1.62) and group B (11.0± 0.83) days. The authors concluded that the addition of Spironolactone hastens and enhances the response to standard treatment with digoxin and chlorothiazide in infants with CHF. Authors suggest that a clinical trial of eplerenone, a selective aldosterone inhibitor, in patients with PLE may be the appropriate next step to answer whether the blocking of aldosterone receptors accounts for spironolactone's diuretic effect and whether long term remission can be achieved.</td>
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**Table 9: Spironolactone use in heart disease**

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<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
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<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
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</thead>
<tbody>
<tr>
<td>Etheridge, 2003, University of Utah</td>
<td>2/8 (11 and 12 years old)</td>
<td>11-52 years</td>
<td>Prospective study</td>
<td>Spirinolactone (3.5±1.2 mg/kg/day) and KCl (3.3±1.5 mEq/kg/day) for four weeks.</td>
<td>None stated</td>
<td>ECG and QT interval analysis</td>
<td>This regimen resulted in an increase in serum potassium from 4.0±0.3 to 5.2±0.3 mEq/L. Therapy was well tolerated without significant side effects</td>
<td>No serious complication was associated with therapy</td>
<td>Long-term oral potassium administration increase serum potassium in patients with long QT syndrome type 2.</td>
</tr>
<tr>
<td>Motz, 2005 Departements of pediatric cardiology, Elisabeth Children’s Hospital, George-Albercht university, George-August university, Germany</td>
<td>20 Infants (10 days-9.2 months)</td>
<td>Retrospective study</td>
<td>Aldactone plus hydrocholorothiazid or furosemide each 1-2 mg/kg/day and digoxin</td>
<td>Same regimen plus beta-blocker (metoprolol or propranolol starting with 0.2-0.5 mg/kg/day and final dose of 1.5-2 mg/kg/day) for 1-2 weeks</td>
<td>Variability in heart rate with reduced neurohumoral stimulation correlated with improved clinical condition.</td>
<td>None stated</td>
<td>No infant suffered any serious side effects, became severely bradycardic, or needed any other additional intervention.</td>
<td>None of these infants, with significant left-to-right shunt, improved while receiving diuretics, spironolactone, and digoxine alone, but improved after the addition of beta blocker (propranolol or metoprolol).</td>
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<tr>
<td>Citation &amp; Date</td>
<td>Study Design</td>
<td>Age range</td>
<td># of patients</td>
<td>Intervention &amp; Dose</td>
<td>Comparison</td>
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<td>Benefits</td>
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| Kaito, 2006, Kobe University Hospital, Japan | Clinical study | 11-19 years | 1/5 patients is within our target population (11 y/o) | Spironolactone 25 mg/day | None stated | Urinary protein/creatinine ratio (U-P/C) and estimated glomerular filtration rates (EGFRs), in other words, the possibility of reducing urinary protein excretion as well as slowing down disease progression with Spironolactone treatment | Spironolactone in addition to angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blocker (ARB) was helpful reducing urinary protein excretion. | There were no adverse events | Before the start of Spironolactone, U-P/C showed no significant reduction but after the start of Spironolactone, U-P/C was significantly reduced at every time point (p<0.05) and gradually reduced to a minimum (0.13±0.06 g/g) at 18 months. EGFR remained virtually unchanged throughout the Spironolactone therapy (before Spironolactone treatment: 129.2±21.4 ml/min and 18 months later 110.1±30.1 ml/min, p=0.115). Blood pressure dropped 3 months after Spironolactone treatment (systolic BP from 110.8±5.0 to 91.2±6.6 mmHg and diastolic BP from 58.2±2.7 to 51.0±3.0 mmHg). Although serum
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<th>Citation &amp; Date</th>
<th>Study Design</th>
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<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
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<td>potassium level was significantly higher 3 months after Spironolactone treatment, none of the patients developed serious hyperkalemia. This study demonstrated that adding Spironolactone to ACEI and ARB may be effective for lowering proteinuria in Alport syndrome. However, a large-scale study with longer follow-up is required to demonstrate whether the results shown in our study translate to improved renal survival for patients with Alport syndrome.</td>
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### Table 11: Spironolactone use in Cystic fibrosis

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<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>May, 1965 A special clinical research unit USA</td>
<td>Observational study</td>
<td>7 months</td>
<td>2</td>
<td>Combination therapy: methopyrapone (125mg/4h) and dexamethasone (0.375mg/8h) and Spironolactone (12.5 mg/6h). Duration of this combination therapy is not stated</td>
<td>Non stated</td>
<td>Relative changes in electrolyte excretion by the sweat glands and the kidneys in cystic fibrosis</td>
<td>Non stated</td>
<td>Non stated</td>
<td>Similar patterns of increased excretion of Na and Cl and changes in K/Na ratio occurred in urine and sweat, but the magnitude percent of change in salt excretion and K/Na were greater for renal excretion</td>
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</table>
### Table 12: Co-administration of Spironolactone with other diuretics in nephritic syndrome

<table>
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<tr>
<th>Citation &amp; Date &amp; Setting</th>
<th>Study Design</th>
<th>Age Range</th>
<th># of Patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes Considered</th>
<th>Benefits</th>
<th>Side Effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kapur, 2009</td>
<td>Prospective Cohort study</td>
<td>Phase one: age range=1.4-15 years</td>
<td>30 Phase one: 10 patients and 8/10 are within our age range. Phase 2: 20 patients and 20/20 are within our age range</td>
<td>VE (intra-vascular volume expansion = fractional excretion of sodium (FeNa) &gt;1%) group received IV furosemide at 1 mg/kg/dose (max 40 mg) twice daily and oral Spironolactone at 2.5 mg/kg/dose twice daily (max 100 mg twice daily, dose around 25 mg tablets or its multiples) for severe oedema</td>
<td>VC (intravascular contraction = FeNa&lt;1%) group received IV albumin (25%) at 0.5 g/kg twice daily over 2-3 hours followed by IV furosemide at 1 mg/kg per dose (max 40 mg) at the end of albumin infusion for severe oedema</td>
<td>Hospital stay and weight loss</td>
<td>None stated</td>
<td>One VE patient in phase 2 who only received diuretic had electrolyte abnormalities and was switched to albumin</td>
<td>There was no difference in hospital stay and weight loss between the VE and VC groups. FeNa is useful in distinguishing VC versus VE in children with nephritic syndrome with severe oedema. The use of diuretics alone in VE patients is safe and effective.</td>
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Table 13: Spironolactone use in hypertrichosis

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<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darendeliler, 1996 Istanbul faculty of medicine, department of pediatrics, Turkey</td>
<td>Clinical trial</td>
<td>Mean age 6.9(1.2) years</td>
<td>12</td>
<td>Spironolactone started at an oral dose of 25 and increased to 100 mg x m (-2) x day8-1) twice daily for one year.</td>
<td>None</td>
<td>Hair growth</td>
<td>Spironolactone therapy was well tolerated and no side effects were observed</td>
<td>No side effects were encountered</td>
<td>Spironolactone may be used safely in the treatment of hypertrichosis. It reduces hair growth to some extent in a number of children.</td>
</tr>
</tbody>
</table>
Table 14: Spironolactone use in mineralocorticoid excess

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<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimartino-Nardi, 1987, New York Hospital-Cornell medical Center, NY</td>
<td>Case series</td>
<td>4-9 years</td>
<td>3</td>
<td>Study 4: Spironolactone 100 mg/day orally for 3 days</td>
<td>Study 1: ACTH(40 units over 360 min) Study 2: Dietary sodium manipulation(low sodium diet 10 mEq/day, high sodium diet 150 mEq/day, regular sodium diet 80 mEq/Day) Study 3: Aldosterone(1 mg/day for 3 days) and hydrocortisone(20 mg/day for 5 days)</td>
<td>Blood pressure</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Spironolactone administration in patient 1 and 2 resulted in fall of BP to the similar level to that achieved with low sodium diet and significantly lower than that achieved with a regular sodium diet. After 3 days of Spironolactone administration, plasma renin activity (PRA) and 24 hour urinary PH1 aldosterone remained suppressed. Continuous IV hydrocortisone administration caused an increase in blood pressure and decrease in serum potassium demonstrating the abnormal mineralocorticoid activity of cortisol in these patients. Addition of Spironolactone resulted in a decrease in BP, rise in serum potassium, and gradual increase in plasma renin activity.</td>
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</table>
## Table 15: Spironolactone Safety

<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
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</thead>
<tbody>
<tr>
<td>Walker. 1964, Newborn Nursery of the Winnipeg General Hospital</td>
<td>Randomized clinical trial</td>
<td>6-47 days</td>
<td>16</td>
<td>3/16 received a single dose of 50 mg Spironolactone</td>
<td>A control urine collection a day before administration of diuretics</td>
<td>24 hour urine flow, Na, K, Cl, Creatinine, CH20</td>
<td>None stated</td>
<td>No clinical side effects were noted</td>
<td>A moderately large increase in urine volume and sodium excretion was observed in the 3 infants who received Spironolactone but the small sample size did not allow statistical analysis. No specific conclusion for Spironolactone was made.</td>
</tr>
<tr>
<td>Atkinson, 1988 Neonatal intensive care unit, McMaster university, Canada</td>
<td>Clinical trial</td>
<td>Infants (gestational age= 26.4±0.6) Postnatal age&gt;1 week</td>
<td>30</td>
<td>Spironolactone alone(2-4 mg/kg/day) n=12</td>
<td>1) Single dose of furosemide(n=6) 2) furosemide plus Spironolactone and hydrochlorothiazide (n=7) 3) Spironolactone(2-4 mg/kg/day) and hydrochlorothiazide(1-2 mg/kg/day) for 5 consecutive days (n=29)</td>
<td>Urinary calcium excretion</td>
<td>None stated</td>
<td>None stated</td>
<td>Hypercalciuria was observed in all but the control group. Treatment with any of these diuretics in neonates may be associated with abnormal renal losses of calcium, sodium, chloride, and potassium. Neonates requiring long term treatment with diuretics, require special consideration, including monitoring of mineral excretion and renal ultrasonography.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Duration</td>
<td>Sample Size</td>
<td>Spironolactone Dose</td>
<td>Serum Potassium Concentration</td>
<td>Adverse Events</td>
<td>Comments</td>
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<td>Buck, 2005, University of Virginia children's Hospital, USA</td>
<td>Prospective Observational study</td>
<td>4 days-21 years</td>
<td>100 (78% &lt;1 year old)</td>
<td>Spironolactone, the average initial dose: 1.8±0.7 mg/kg/day (range 0.5-4.2) once (n=53) or twice (n=43) a day. Two subjects received doses every 8 hours and two other subjects received doses every 6 hours. Patients with chronic lung disease received higher initial dose than those with heart disease (2±0.8 vs. 1.7±0.5 mg/kg/day). 66 patients received furosemide, 37 received thiazides and 12 received both.</td>
<td>None stated</td>
<td>Serum potassium concentration</td>
<td>Not stated</td>
<td>The average serum potassium level after initiation of treatment was (4.3±0.8 mEq/L with higher values in patients with CLD vs. HD (4.7±0.7 vs., 4.2±0.7 mEq/L) This study showed that Spironolactone was a frequent part of combination diuretic regimen used in the management of pediatric cardiac and pulmonary disease. The most common adverse effect was alteration in serum potassium level, resulting from the combined effects of Spironolactone with other diuretics, aspirin, or ACEI. While hyperkalemia was more common initially, hypokalemia was a more significant problem with long-term diuretic use. Potassium concentrations should be carefully monitored, particularly in children receiving multiple diuretics. Additional research is needed to define the pharmacokinetics and optimal dosing interval of Spironolactone, as well as determine its long-term effects on potassium.</td>
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<td>Jenis, 1969, Retrospect</td>
<td>5-75</td>
<td>15(2/15)</td>
<td>Spironolactone</td>
<td>None stated</td>
<td>Adrenal</td>
<td>None</td>
<td>None</td>
<td>Distinctive laminated intracytoplasmic</td>
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Walter Reed General Hospital, Washington, DC

Inclusions develop in the human adrenal gland following prolonged Spironolactone therapy. The result of this study suggests a hypothesis: as a consequence of chronic administration of Spironolactone and the sodium diuresis which ensues, there is an activation of the endogenous renin-angiotensin system. Since Spironolactone is a synthetic foreign steroidal compound, it may interfere with the normal membrane turnover causing a progressive accumulation of granular membranes and exaggeration of normal phenomenon.
Table 16: Co-administration of Spironolactone with other diuretics in infants with lung disease

<table>
<thead>
<tr>
<th>Citation &amp; Date &amp; setting</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kao, 1987 Intensive care Nursery at Oakland Children's Hospital, California</td>
<td>Double-blind cross over trial</td>
<td>Infants (gestational age = 28.5±3.4 weeks)</td>
<td>Group 1 (n=10) received successively placebo, theophylline, and theophylline plus diuretics (chlorothiazide 20mg/kg/dose combined with Spironolactone 1.5 mg/kg/dose twice daily)</td>
<td>Group 2 (n=9) Received theophylline, placebo, and placebo plus diuretics (chlorothiazide 20mg/kg/dose combined with Spironolactone 1.5 mg/kg/dose twice daily) on successive 4-day periods.</td>
<td>PFT at the start of the study and at the end of each 4-day period</td>
<td>There was no difference between the fluid intake of the two groups. No infants required supplemental diuretics or bronchodilators during the study.</td>
<td>None stated</td>
<td>This study showed that oral diuretics and theophylline have synergistic effects in infants with BPD (improved airway resistance, dynamic compliance, maximal expiratory flow at functional residual capacity, and time constant at functional residual capacity significantly more than theophylline alone). The authors suggest that combined orally administered diuretics and theophylline are of benefit in some infants with BPD.</td>
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