

Alert	Avoid in preterm neonates until term corrected age for the treatment of hypertension due to concern of impaired kidney development, hyperkalemia and acute kidney injury.(1). May cause rapid drop in BP.(1-3)
Indication	Congestive heart failure Treatment of hypertension: Calcium channel blockers (e.g. Amlodipine) or peripheral vasodilators (hydralazine) are better alternatives. Congenital nephrotic syndrome – To reduce proteinuria.(4-6)
Action	Angiotensin-converting enzyme inhibitor (ACEI). Heart failure: Peripheral vasodilator - Reduces afterload (blood pressure (BP) and systemic vascular resistance) and preload (right atrial pressure and left ventricular filling pressure) and increases cardiac output. Hypertension: Several mechanisms of action: (1) inhibits formation of angiotensin II, (2) decreases bradykinin degradation and, (3) inhibits norepinephrine release from sympathetic nerve endings. All these effects produce significant vascular relaxation, reduction of after-load and improvement in cardiac output. Proteinuria: The mechanism of the anti-proteinuric effect is not clearly understood. Reduction of systemic and intraglomerular pressures and improved size selectivity of glomerular basement membrane have been proposed.(7) Proteinuria reduction may also occur by a dose dependent hemodynamic effect on the efferent arteriole which can result additionally in reduction of glomerular filtration rate (GFR). (8)
Drug type	Angiotensin-converting enzyme inhibitor (ACEI).
Trade name	Capoten
Presentation	5mg/mL oral solution.
Dose	Hypertension Starting dose: 0.01-0.1 mg/kg/dose 8 hourly. First dose may cause rapid drop in BP.(1) Maintenance dose: 0.01–0.5 mg/kg/dose 8 hourly.(1) Congestive heart failure Starting dose: 0.05-0.1 mg/kg 8 hourly (lower range if combined with diuretics or other vasoactive agents) Maintenance dose: 0.1 mg/kg/dose 8 hourly and titrate to 0.3 mg/kg/dose 8 hourly** *Doses up to 2 mg/kg/dose 8 hourly are used in children (9). #6-hourly frequency (but with same daily dose) may occasionally be used at the discretion of cardiology. Congenital nephrotic syndrome Starting dose: 0.1 – 0.3 mg/kg/dose 8 hourly. Gradually increase to 1-2 mg/kg/dose 8 hourly (4)
Dose adjustment	Therapeutic hypothermia – No information. ECMO – No information. Renal impairment - If GFR >50 ml/min/1.73m ² – no dose adjustment is needed. If GFR 10-50 ml/min/1.73m ² – 50% of recommended dose. If GFR <10 ml/min/1.73m ² – Avoid it (ANMF consensus) Hepatic impairment – No studies to recommend dose adjustment but hepatic failure is known in adults.
Maximum dose	Hypertension: 2 mg/kg/day (1) Nephrotic syndrome: 6 mg/kg/day (4)
Total cumulative dose	Not applicable
Route	Oral
Preparation	Dilute 1 mL (= 5mg) of captopril 5 mg/mL oral solution with 4 mL of water for injection to make 1 mg/mL solution
Administration	ORAL before feeds
Monitoring	Close monitoring of blood pressure – BP is measured at 10 minute intervals for 30-40 minutes following the first dose and 15 and 30 minutes following the first dose of any increase in dosage. BP is monitored twice daily once a maintenance dose is achieved. Regular monitoring of serum potassium and creatinine (1)

	White cell count (neutropenia) Watch for angioedema
Contraindications	Severe renal impairment Hypersensitivity to captopril or components of the formulation. Angioedema. Preterm neonates until term corrected age, because of impaired nephrogenesis risk (1) (ANMF consensus)
Precautions	Neutropenia Renal impairment
Drug interactions	ACE-inhibitors will increase the effect of diuretics. Combination of ACE inhibitor, diuretic and NSAID may precipitate acute renal failure. Potassium supplements or drugs which increase potassium level (eg spironolactone) – risk of hyperkalaemia Antihypertensive medications in combination with captopril will increase risk of hypotension.
Adverse reactions	Hypotension Neutropenia, agranulocytosis Hyperkalemia, raised serum creatinine and renal failure(2, 3) Angioedema and anaphylaxis Hepatic impairment Isolated dry cough in infants and children(10)
Compatibility	Not applicable
Incompatibility	Not applicable
Stability	28 days after opening.
Storage	Store in refrigerator at 2-8°C.
Excipients	Citric acid, sodium citrate dihydrate, disodium edetate, sodium benzoate and water (pH adjusted with sodium hydroxide and hydrochloric acid)
Special comments	
Evidence	<p>Efficacy</p> <p>Hypertension O’dea et al, in a small retrospective study of neonates found an initial dose of 0.01 mg/kg was effective.(2) Tack et al, in their retrospective study of sick premature infants with chronic lung disease who received captopril (0.3 mg/kg) for systemic hypertension noted significant fall in BP after the initial dose necessitating halving the dose subsequently. Some of the infants developed oliguria and neurologic signs (seizures, lethargy, apneas) with fall in BP.(3) Gantenbein et al investigated side effects of captopril in 43 newborn and young infants with congenital heart disease after cardiac surgery treated with captopril for heart failure.(11) Initial median dose of captopril was 0.17 mg/kg/day (range 0.05-0.55 mg/kg/day), slowly increased over 3-33 days to a maximal median dose of 1.86 mg/kg/day (range 0.2-2.3 mg/kg/day). All patients were simultaneously treated with diuretics. They reported renal impairment, hypotension and desaturations. These side effects were not dose related and all were reversible.</p> <p>Heart failure ACEIs prevent, attenuate, or possibly reverse the pathophysiological myocardial remodeling. In addition, they decrease afterload by antagonizing the rennin-angiotensin-aldosterone system.(9) The International Society of Heart and Lung Transplantation on the management of paediatric heart failure recommends ACEIs in all patients with heart failure and left ventricular systolic dysfunction. Therapy with ACE inhibitors should be started at low doses with a subsequent up-titration to the target dose with careful monitoring of blood pressure, renal function, and serum potassium.(9,12)</p> <p>Congenital nephrotic syndrome ACEI and prostaglandin inhibitors have been shown to reduce proteinuria. The effect of ACEI reaches optimal after 4-8 weeks of treatment. A combination of captopril and indomethacin was successfully used (4-6). In a case series, Kovacevic et al reported young infants with congenital nephrotic syndrome treated with unilateral nephrectomy, captopril and indomethacin. Treatment with captopril and indomethacin was commenced at a median age of 2.3 months (range 0.2–5.2 months),</p>

	<p>and was given prior to unilateral nephrectomy in six children and 2 weeks after unilateral nephrectomy in one child. Captopril was started at a low median dose of 0.3 (range 0.3–0.75) mg/kg per day divided in three doses and gradually increased to a maximum median dose of 3.4 (range 1.0–6.0) mg/kg per day. The initial median dose of indomethacin was 0.8 (range 0.3–1.2) mg/kg per day divided in two doses given to a maximum median dose of 2.8 (range 1.2–3.0) mg/kg per day.(4)</p> <p>Pharmacokinetics Onset of action is within 15 minutes with a maximum effect in 1-2 hours. Most of the drug is eliminated through kidneys.(2, 3, 11, 13)</p>
<p>Practice points</p>	<p>Hypertension Captopril is not recommended as the first line antihypertensive agent for neonatal hypertension because of concerns with kidney development and other side effects.(GOR B, LOE IV) (1-3, 11)</p> <p>Heart failure ACE inhibitors are recommended in all patients with HF and left ventricular systolic dysfunction. Therapy with ACE inhibitors should be started at low doses with a subsequent up-titration to the target dose with careful monitoring of blood pressure, renal function, and serum potassium.(9,12) ACE inhibitors are considered relatively safe for children with heart failure irrespective of etiology of heart failure, but renal impairment, hypotension and hyperkalemia are common adverse reaction.(14) This treatment is based on the assumption that blocking of the renin-angiotensin-aldosterone system has a positive effect on morbidity and mortality, as it does in adults with heart failure. The dose of captopril ranged from 0.07-2.5 mg/kg/day with a duration of treatment up to 3 years. (15,16)</p>
<p>References</p>	<ol style="list-style-type: none"> 1. Flynn JT, editor The hypertensive neonate. Seminars in Fetal and Neonatal Medicine; 2020: Elsevier. 2. O'Dea RF, Mirkin BL, Alward CT, Sinaiko AR. Treatment of neonatal hypertension with captopril. The Journal of pediatrics. 1988;113(2):403-6. 3. Tack ED, Perlman JM. Renal failure in sick hypertensive premature infants receiving captopril therapy. The Journal of pediatrics. 1988;112(5):805-10. 4. Kovacevic L, Reid CJ, Rigden SP. Management of congenital nephrotic syndrome. Pediatric Nephrology. 2003 May;18(5):426-30. 5. Heaton PA, Smales O, Wong W. Congenital nephrotic syndrome responsive to captopril and indometacin. Archives of disease in childhood. 1999 Aug 1;81(2):174-5. 6. Pomeranz A, Wolach B, Bernheim J, Korzets Z. Successful treatment of Finnish congenital nephrotic syndrome with captopril and indomethacin. The Journal of pediatrics. 1995 Jan 1;126(1):140-2. 7. Bagga A, Mudigoudar BD, Hari P, Vasudev V. Enalapril dosage in steroid-resistant nephrotic syndrome. Pediatric Nephrology. 2004;19(1):45-50. 8. Heeg JE, de Jong PE, van der Hem GK, de Zeeuw D. Reduction of proteinuria by angiotensin converting enzyme inhibition. Kidney international. 1987 Jul 1;32(1):78-83. 9. Masarone D, Valente F, Rubino M, Vastarella R, Gravino R, Rea A, et al. Pediatric Heart Failure: A Practical Guide to Diagnosis and Management. Pediatrics & Neonatology. 2017;58(4):303-12. 10. von Vigier RO, Mozzettini S, Truttmann AC, Meregalli P. Cough is common in children prescribed converting enzyme inhibitors. Nephron. 2000;84(1):98. 11. Gantenbein MH, Bauersfeld U, Baenziger O, Frey B, Neuhaus T, Sennhauser F, et al. Side effects of angiotensin converting enzyme inhibitor (captopril) in newborns and young infants. Journal of perinatal medicine. 2008;36(5):448-52. 12. Kirk R, Dipchand AI, Rosenthal DN, Addonizio L, Burch M, Chrisant M, et al. The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: Executive summary. The Journal of Heart and Lung Transplantation. 2014;33(9):888-909. 13. Pereira CM, Tam YK, Collins-Nakai RL. The pharmacokinetics of captopril in infants with congestive heart failure. Therapeutic drug monitoring. 1991;13(3):209-14. 14. Momma K. ACE inhibitors in pediatric patients with heart failure. Pediatric Drugs. 2006;8(1):55-69. 15. Jovanovic I, Lagler F, Kingmann I, Laer S, de Wildt S. How safe are ACE inhibitors for heart failure in children? Children with Dilated Cardiomyopathy. 2018;103(1):97. 16. Van Der Meulen M, Dalinghaus M, Burch M, Szatmari A, Diez CC, Khalil F, et al. Question 1: How safe are ACE inhibitors for heart failure in children? Archives of disease in childhood. 2018;103(1):106-9.

VERSION/NUMBER	DATE
Original 1.0	18/11/2021
Version 2.0	25/11/2021
Revised 3.0	17/02/2022
REVIEW	17/02/2027

Authors Contribution

Original author/s	Anke Raaijmakers, Srinivas Bolisetty
Evidence Review	Srinivas Bolisetty
Expert review	Fiona Mackie, Hiroko Asakai
Nursing Review	Kirsty Minter, Eszter Jozsa, Priya Govindaswamy
Pharmacy Review	Mohammad Irfan Azeem, Michelle Jenkins
ANMF Group contributors	Nilkant Phad, Bhavesh Mehta, John Sinn, Helen Huynh, Simarjit Kaur, Joanne Malloy, Hannah Bell
Final editing	Thao Tran
Electronic version	Cindy Chan, Ian Callander
Facilitator	Srinivas Bolisetty

NEW RELEASE