Conditions Associated with Hypertension in a High-risk Premature Infant

June-Ming Chen[1,2], Mei-Jy Jeng[1,2,3]*, Shih-Yun Chiu[1,2], Yu-Sheng Lee[1,2,3], Wen-Jue Soong[1,2,3], Betau Hwang[1,2,3], Ren-Bin Tang[1,2]

[1]Department of Pediatrics, Taipei Veterans General Hospital, [2]Department of Pediatrics and [3]Institute of Emergency and Critical Care Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

Hypertension is an uncommon but significant problem in high-risk neonates and infants, and the spectrum of potential causes is broad. Here, we describe an extremely premature infant (birth weight, 728 g; gestational age, 27 weeks) with multiple complications and hypertension. During admission, umbilical artery catheters were used for a period of time, and he suffered from respiratory distress syndrome, intraventricular hemorrhage, pulmonary hemorrhage, patent ductus arteriosus, pericardial effusion, heart failure, repeated sepsis, anemia, thrombocytopenia, chronic lung disease, and progressive liver damage. He was treated with multiple medications, including erythropoietin, indomethacin, epinephrine, dopamine, aminophylline, multiple antibiotics, amphotericin B, and total parenteral nutrition. Hypertension was first noted when he was 41 days old, with spontaneous remission. It then recurred, reaching higher than 100 mmHg when he was almost 4 months old. After stopping erythropoietin, hypertension subsided for a short period of time and went up again. Multiple factor-related hypertension in this premature infant was considered. Related literature on hypertension in premature infants is reviewed. In conclusion, multiple factors can influence blood pressure and may induce hypertension in high-risk premature infants. Thus, blood pressure should be closely monitored in high-risk premature infants. Judicious use of all medications and interventions are crucial to decrease the incidence of hypertension in high-risk premature infants. [*J Chin Med Assoc* 2008;71(9):485–490]

Key Words: high-risk, hypertension, medication, premature infant

Introduction

Hypertension is an uncommon but significant problem in neonates and infants. The incidence of hypertension in neonates is not high, with published incidence ranging from 0.2% to 3%.[1,2] Hypertension in neonates or infants may develop secondary to complications of catheterization, certain medications, or be a sign of an underlying renal or cardiac disease. In most cases, hypertension may resolve, but some infants may require long-term treatment.[2]

Here, we report a high-risk premature infant who suffered from hypertension and discuss his possible related medications and underlying diseases.

Case Report

This male infant was extremely premature, born with emergent cesarean section due to maternal abruptio placenta. His Apgar scores were 4 at 1 minute and 6 at 5 minutes. Gestational age was 27 weeks, and his birth weight was only 728 g.

Reviewing the medical history of this premature infant during admission, there were multiple serious problems, including respiratory distress syndrome, intraventricular hemorrhage, pulmonary hemorrhage, patent ductus arteriosus (PDA), pericardial effusion, heart failure, hypertension, repeated sepsis, anemia, thrombocytopenia, chronic lung disease, and progressive liver damage.

*Correspondence to: Dr Mei-Jy Jeng, Department of Pediatrics, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: mjjeng@vghtpe.gov.tw • Received: February 20, 2008 • Accepted: April 30, 2008

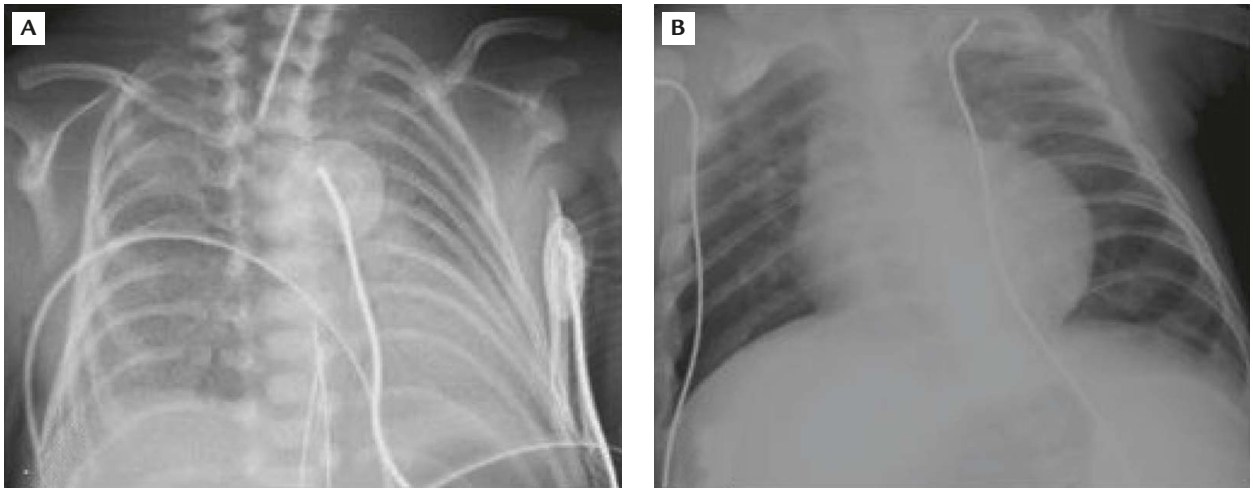

Figure 1. Chest X-ray films for the premature infant: (A) appearance of ground-glass pattern at 1 day of age; (B) cardiomegaly and chronic lung disease at 150 days of age.

Due to respiratory distress syndrome with respiratory failure (Figure 1A), the patient had been intubated and treated with exogenous surfactant and high-frequency oscillatory ventilation since birth. Umbilical arterial and venous lines were inserted for 16 and 14 days, respectively. He had been ventilated for 17 days initially and reintubated for the following 22 days because of respiratory failure complicated with severe pulmonary hemorrhage, PDA, heart failure, sepsis, upper gastrointestinal bleeding and unstable vital signs. In addition, he was intubated again for 4 days due to sepsis when he was 4 months old. Between and after intubations, his respiration was supported with oxygen by nasal-prong continuous positive airway pressure (CPAP) or nasal cannula until discharge. Therefore, the respiratory conditions are compatible with the diagnosis of chronic lung disease (CLD) and/or bronchopulmonary dysplasia (BPD).

Hypotension with low blood pressure (39/19 mmHg) was found early after birth, and dopamine was used to maintain blood pressure and renal blood flow (Figures 2 and 3). Unfortunately, significant hypertension was noted when the patient was 41 days old, with a peak systolic blood pressure (SBP) of 125 mmHg. Figure 2 shows the average SBP and diastolic blood pressure (DBP) of the infant on each day of his admission. SBP spontaneously returned to lower than 100 mmHg 4 days later. However, high SBP (>100 mmHg) was observed occasionally when the infant was 116 days old, and persisted before discharge. During that period, there were 16 days (16.8%) when SBP was higher than 100 mmHg and 70 days (73.7%) when it was higher than 90 mmHg (Figure 2).

Due to anemia, the patient received multiple transfusions of packed red blood cells. In addition, erythropoietin (EPO) injection was also used when the

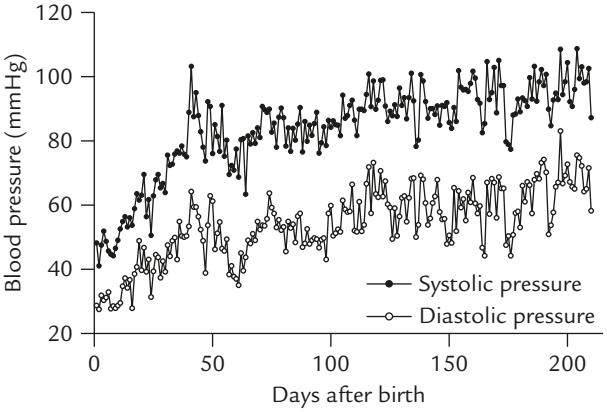

Figure 2. Average daily systolic and diastolic blood pressures of the premature infant during hospitalization.

infant was 92–106 days old and 151–173 days old (mean dosage of EPO, 580–710 IU/kg/week). SBP was around 76–94 mmHg during the 1st period of time, and 83–105 mmHg during the 2nd period of time. After consultation with a pediatric nephrologist, possible hypertension caused by the use of EPO was considered. Therefore, the use of EPO was stopped. Serum renin measured before EPO was stopped was 46.20 pg/mL; it had decreased to 19.57 pg/mL 2 weeks later. Renal Doppler ultrasonography also showed normal blood flow over bilateral kidneys. With the use of captopril, SBP decreased to lower than 90 mmHg. However, blood pressure went back to being unstable after stopping captopril. The use of EPO, captopril, and all possible related medications are shown in Figure 3A.

PDA and pulmonary hypertension had been diagnosed by cardiac ultrasonography when the patient was 2 days old. He was treated with fluid restriction,

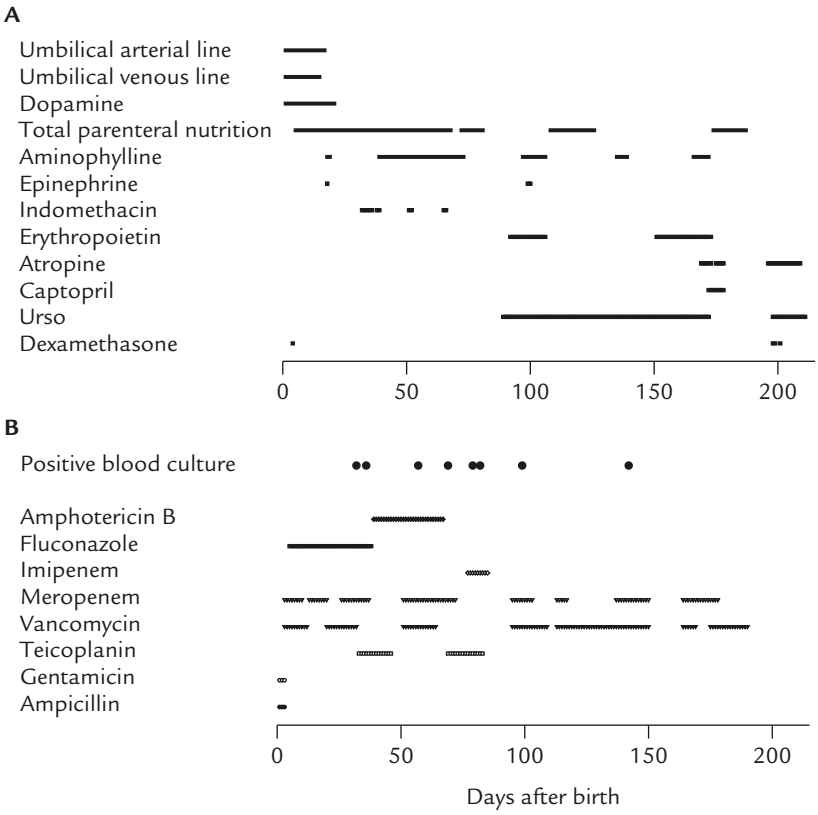

Figure 3. Umbilical catheterizations and medications in the premature infant during hospitalization.

but indomethacin was not given until he was 30 days old because of massive pulmonary hemorrhage, gastric bleeding, sepsis, and unstable vital signs during the 1st month of life. Since cardiac ultrasonography still showed PDA (0.21 cm) with the presence of minimal pericardial effusion, indomethacin was given (0.2 mg/kg/dose, 3 doses/course) for 2 courses between 31 and 35 days of age. After that, the PDA was found to be closed, but opened again 3 times. Therefore, indomethacin was used for another 3 courses between the age of 37 and 65 days (Figure 3A). Unfortunately, reopened PDA (residual duct 0.1 cm) with pericardial effusion (0.2–0.3 cm) was still observed when the patient was 100 days old. Cardiomegaly and pericardial effusion were both persistently observed. Chest X-ray taken when he was 150 days old revealed significant cardiomegaly (Figure 1B).

Repeated infections, including bacteremia, pneumonia, and fungemia were found in this extremely premature infant. During hospitalization, he needed multiple antimicrobial drugs to control infections, including fluconazole, amphotericin B, vancomycin, teicoplanin, meropenem, and imipenem (Figure 3B). The proven organisms included *Candida tropicalis*, *Staphylococcus capitis*, *Staphylococcus epidermidis*, coagulase-negative *Staphylococcus*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Escherischia coli*.

Because of extreme prematurity, poor intestinal absorption of breast milk and semi-elemental formula, he received total parenteral nutrition (TPN) for a long time. However, body weight gain was seriously interrupted by the episodes of sepsis. TPN-related cholestatic jaundice, hepatomegaly and complication with cirrhotic change occurred gradually.

The patient was transferred to the intermediate nursery when he was 7 months of age and was discharged 1 week later (215 days old; weight, 1,765 g).

Unfortunately, he was admitted again 2 weeks later due to respiratory distress, suspected sepsis, and hepatic failure with massive ascites. His SBP was around 85–110 mmHg and DBP was around 55–80 mmHg when his condition was stable. However, sick sinus syndrome and intractable hypoglycemia were later found. He died 2 months later with multiorgan failure.

Discussion

Neonatal hypertension is an uncommon but significant complication in intensive cases. Although the incidence

of hypertension in neonates and infants is low, premature and sick infants are at high risk.[3] Hypertension in neonates and premature infants is best defined as SBP and/or DBP higher than the 95th percentile for those infants' age and gender.[3,4] Studies in both term and preterm infants have demonstrated that blood pressure in neonates increases with gestational, postconceptual age, and birth weight.[4–6] According to this, the presented case definitely experienced hypertension at the age of 41 days. During the later stage (between 116 and 215 days old), the infant's corrected age was 1–4 months old. The 95th percentile of SBP for that age in male infants is 105–110 mmHg.[7] Even though the SBP was not higher than 110 mmHg, 16% of that duration had SBP higher than 100 mmHg. Thus, the diagnosis of hypertension of this presented case is controversial because of his relatively low body weight (around 1,600–1,800 g) during that period of time. Therefore, considerations of both age and body weight are crucial for the diagnosis and treatment of hypertension in young infants.

The causes of hypertension in neonates are numerous, with the 2 largest categories being renovascular and other renal parenchymal diseases.[8–11] The possible etiologies of neonatal hypertension are summarized from reported articles and listed in Table 1.[3,9–20] As shown, umbilical artery catheter-associated thromboembolism affecting either the aorta and/or renal arteries probably accounts for the majority of cases of hypertension seen in the typical neonatal intensive care unit (NICU). A clear association between use of umbilical arterial catheters and development of arterial thrombi was demonstrated in the early 1970s by Neal et al.[12] In our case, an umbilical catheter was inserted for a total of 16 days, so there is probably a high correlation with his hypertension.

Hypertension has been reported to be a consequence of BPD.[13,14] In a study of 65 infants discharged

Table 1. Conditions associated with hypertension in neonates and infants[3,9–20]

Renovascular hypertension
- Aortic or renal thromboembolism related to umbilical artery catheterization
- Congenital stenosis or hypoplasia of renal or aortic artery
- Compression of renal artery
- Idiopathic arterial calcification

Renal causes of hypertension

Congenital
- Polycystic kidney disease
- Renal hypoplasia
- Hydronephrosis

Acquired diseases
- Renal obstruction following surgical correction
- Acute tubular necrosis
- Interstitial nephritis
- Acute renal failure

BPD (chronic lung disease)

Genetic causes

Single-gene disorder
- Liddle's syndrome
- Pseudohypoaldosteronism type II

Malformation syndrome
- William's syndrome (renal artery stenosis)
- Turner's syndrome (aortic coarctation)

Cardiovascular
- Coarctation of thoracic aorta
- PDA

Surgical repair of an abdominal wall defect

Endocrine disorder
- Congenital adrenal hyperplasia
- Hyperaldosteronism
- Hyperthyroidism

Tumors
- Neuroblastoma
- Wilms' tumor

Neurologic causes
- Intracranial hypertension
- Drug withdrawal
- Seizure

Iatrogenic causes
- Hypervolemia secondary to excess administration of sodium or fluids

Medications
- Dexamethasone
- Pancuronium
- Indomethacin
- Adrenergic agents
- Theophylline
- Caffeine
- Vitamin D intoxication
- Phenylephrine
- Erythropoietin?
- Amphotericin B?

ECMO

Antenatal factors
- Antenatal steroid administration
- Maternal hypertension

BPD = bronchopulmonary dysplasia; PDA = patent ductus arteriosus; ECMO = extracorporeal membranous oxygenation.

from a NICU, the incidence of hypertension in infants with BPD was 43%, versus an incidence of 4.5% in infants without BPD.[13] Investigators were unable to identify a clear cause of hypertension, but postulated that hypoxemia might be involved. Over half of the infants with BPD who developed hypertension did not manifest it until discharged from the NICU, highlighting the need for measurement of blood pressure in NICU "graduates", whether or not they have lung disease.[21] Alagappan and Malloy also found that hypertension was twice as common in very low-birth weight infants with BPD compared to the incidence in all very low-birth weight infants.[14] Development of hypertension appeared to be correlated with the severity of pulmonary disease, as all of the hypertensive infants required supplemental oxygen and aminophylline. A greater need for diuretics and bronchodilators has also been shown to correlate with the development of hypertension in infants with severe BPD.[15] Our case needed long-term intubation with mechanical ventilation, nasal CPAP, and oxygen support for more than 7 months. BPD and/or CLD is a definite diagnosis. Thus, BPD likely contributed to his hypertension during the later period of admission.

Hypertension in high-risk premature infants may also develop later, even following discharge from the NICU. In 1987, Friedman and Hustead reported hypertension (defined as SBP > 113 mmHg on 3 consecutive visits over 6 weeks) in 2.6% of infants discharged from their NICU.[21] The diagnosis of hypertension was made in these infants at a mean corrected age of approximately 2 months. Infants in this study who developed hypertension tended to have lower initial Apgar scores and slightly longer NICU stays than infants who remained normotensive, indicating that sicker babies have a greater risk of developing hypertension. Although the number of babies affected is likely to be relatively small, blood pressure screening has been suggested to be included in the follow-up of NICU graduates, especially those with more complicated NICU courses.[21] Our case also had a low Apgar score and very critical conditions since birth; therefore, he was at a high risk of developing hypertension.

There have been many drugs reported to be related with neonatal hypertension (Table 1). Dexamethasone and aminophylline were the most often reported to have correlations to neonatal hypertension.[16] In addition, high doses of adrenergic agents, prolonged use of pancuronium, or administration of phenylephrine ophthalmic drops were also reported to raise blood pressure in neonates.[17] Such hypertension typically resolves when the offending agent is discontinued or its dose reduced. For infants receiving prolonged TPN, hypertension may result from salt and water overload, or from hypercalcemia caused either directly by excessive calcium intake, or indirectly by vitamin A or D intoxication. In our case, multiple drugs had been used, including adrenergic drugs, aminophylline, indomethacin, dexamethasone and long-term TPN (Figure 3A). All of them may relate to the elevation of blood pressure.

Also, hypertension in our case during the later stage was observed after the use of EPO for a period of time. With the finding of elevated serum renin concentrations, EPO-related hypertension was also considered, and the hypertension seemed to improve after EPO was stopped. Although there have been some reports of EPO-related hypertension in adult uremia cases,[22,23] EPO-associated neonatal hypertension is rare.[24–26] Since EPO has been recognized worldwide as a regular therapy to reduce red blood cell transfusions in extremely premature infants,[24–26] possible EPO-related hypertension should be considered in these premature infants.

Furthermore, amphotericin B should be considered to be a hypertensive factor because it was used for 1 month in this infant. Although there were no previous case reports of neonates, 2 adults were reported to have amphoterin B-associated hypertension.[27,28] Our patient was also treated with multiple antibiotics (Figure 3B) to control infections,[29] so infection-induced interstitial nephritis or nephrotoxicity induced by some antibiotics should also be considered as contributing factors.

Reviewing the medical history of this presented case, there must be multiple factors that contributed to his hypertension, including umbilical catheter placement, CLD/BPD, unclosed PDA, sepsis and the use of indomethacin, aminophylline, adrenergic agents, EPO, antibiotics, amphotericin B, dexamethasone, and TPN. All these medications and interventions may relate to his hypertension.[9–19]

In conclusion, multiple factors can influence blood pressure and may induce hypertension in high-risk premature infants. Thus, blood pressure should be checked in high-risk neonates, and even after their discharge from NICU. Judicious use of all medications and interventions are crucial to decrease the incidence of hypertension in high-risk premature infants.

References

1. Rajpoot D, Duel B, Thayer K, Shanberg A. Medically resistant neonatal hypertension: revisiting the surgical causes. *J Perinatol* 1999;19:582–3.
2. Flynn J. Neonatal hypertension: diagnosis and management. *Pediatr Nephrol* 2000;14:332–41.
3. Nafday SM, Brion LP, Benchimol C, Satlin LM, Flynn JT, Edelmann CM Jr. Renal disease. In: MacDonald MG, Mullett

MD, Seshia MMK, eds. *Avery's Neonatology Pathophysiology & Management of the Newborn,* 6th Edition. Philadelphia: Lippincott Williams & Wilkins, 2005:1016–23.
4. Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group. *J Perinatol* 1995;15:470–9.
5. Versmold HT, Kitterman JA, Phibbs RH, Gregory GA, Tooley WH. Aortic blood pressure during the first 12 hours of life in infants with birth weight 610 to 4,220 grams. *Pediatrics* 1981; 67:607–13.
6. Tan KL. Blood pressure in very low birth weight infants in the first 70 days of life. *J Pediatr* 1988;112:266–70.
7. Bernstein D. The cardiovascular system. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. *Nelson Textbook of Pediatrics*, 18th edition. Philadelphia: Saunders Elsevier, 2007: 1860–1.
8. Inglefinger JR. Hypertension in the first year of life. In: Portman RJ, Sorof JM, Ingelfinger JR, eds. *Pediatric Hypertension.* Philadelphia: Saunders Elsevier, 2004:229–40.
9. Buchi KF, Siegler RL. Hypertension in the first month of life. *J Hypertens* 1986;4:525–8.
10. Skalina MEL, Kliegman RM, Fanaroff AA. Epidemiology and management of severe symptomatic neonatal hypertension. *Am J Perinatol* 1986;3:235–9.
11. Singh HP, Hurley RM, Myers TF. Neonatal hypertension: incidence and risk factors. *Am J Hypertens* 1992;5:51–5.
12. Neal WA, Reynolds JW, Jarvis CW, Williams HJ. Umbilical artery catheterization: demonstration of arterial thrombosis by aortography. *Pediatrics* 1972;50:6–13.
13. Abman SH, Warady BA, Lum GM, Koops BL. Systemic hypertension in infants with bronchopulmonary dysplasia. *J Pediatr* 1984;104:929–31.
14. Alagappan A, Malloy MH. Systemic hypertension in very low-birth weight infants with bronchopulmonary dysplasia: incidence and risk factors. *Am J Perinatol* 1998;15:3–8.
15. Anderson AH, Warady BA, Daily DK, Johnson JA, Thomas MK. Systemic hypertension in infants with severe bronchopulmonary dysplasia: associated clinical factors. *Am J Perinatol* 1993;10:190–3.
16. Greenough A, Emery EF, Gamsu HR. Dexamethasone and hypertension in preterm infants. *Eur J Pediatr* 1992;151:134–5.
17. Greher M, Hartmann T, Winkler M, Zimpfer M, Crabnor CM. Hypertension and pulmonary edema associated with subconjunctival phenylephrine in a 2-month old child during cataract extraction. *Anesthesiology* 1998;88:1394–6.
18. Baenziger O, Waldvogel K, Ghelfi D, Arbenz U, Fanconi S. Can dopamine prevent the renal side effects of indomethacin? A prospective randomized clinical study. *Klin Padiatr* 1999; 211:438–41.
19. Evans N, Iyer P. Change in blood pressure after treatment of patent ductus arteriosus with indomethacin. *Arch Dis Child* 1993;68:584–7.
20. Seliem WA, Falk MC, Schdbolt B, Kent AL. Antenatal and postnatal risk factors for neonatal hypertension and infant follow-up. *Pediatr Nephrol* 2007;22:2081–7.
21. Friedman AL, Hustead VA. Hypertension in babies following discharge from a neonatal intensive care unit. *Pediatr Nephrol* 1987;1:30–4.
22. Jurado García JM, Torres Sánchez E, Olmos Hidalgo D, Alba Conejo E. Erythropoietin pharmacology. *Clin Transl Oncol* 2007;9:715–22.
23. Annuk M, Linde T, Lind L, Fellström B. Erythropoietin impairs endothelial vasodilatory function in patients with renal anemia and in healthy subjects. *Nephron Clin Pract* 2006; 102:c30–4.
24. Klipp M, Holzwarth AU, Poeschl JM, Nelle M, Linderkamp O. Effects of erythropoietin on erythrocyte deformability in non-transfused preterm infants. *Acta Paediatr* 2007;96: 253–6.
25. Ohlsson A, Aher SM. Early versus late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. *Cochrane Database Syst Rev* 2006;3:1–23.
26. Ohls RK, Ehrenkranz RA, Wright LL, Lemons JA, Korones SB, Stoll BJ, Stark AR, et al. Effects of early erythropoietin therapy on the transfusion requirements of preterm infants below 1250 grams birth weight: a multicenter, randomized, controlled trial. *Pediatrics* 2001;108:934–42.
27. Rodrigues CA, Yamamoto M, Arantes Ade M, Chauffaille Mde L, Colombo AL, Bordin JO. Amphotericin B-induced severe hypertension in a young patient: case report and review of the literature. *Ren Fail* 2006;28:185–7.
28. Le Y, Rana KZ, Dudley MN. Amphotericin B-associated hypertension. *Ann Pharmacother* 1996;30:765–7.
29. Lee NC, Chen SJ, Tang RB, Hwang BT. Neonatal bacteremia in a neonatal intensive care unit: analysis of causative organisms and antimicrobial susceptibility. *J Chin Med Assoc* 2004;67: 15–20.