Prematurity

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INTRODUCTION

PREMATURITY is defined as birth before 37 weeks' gestation, with very preterm infants being born before 32 weeks and those classified as extremely preterm born before 28 weeks, according to the WHO.[1]

Premature birth affects approximately 9% of pregnancies in Australia and is the largest cause of mortality and morbidity for newborn infants.[2] Most preterm infants are born between 32 and 36 completed weeks of gestation (moderate-to-late preterm); only 0.9% of all births are extremely preterm.[3]

The most common causes of prematurity are spontaneous preterm labour followed by elective preterm delivery for pathologies that include pre-eclampsia, fetal growth restriction, congenital anomalies and severe maternal disease.[4] Preterm prolonged rupture of the membranes and multiple pregnancy also make a significant contribution.[4]

The costs of prematurity over the life course are difficult to quantify but run into millions of dollars, in part because there is a significant risk of neurodevelopmental sequelae. Recently, the costs of prematurity early in life have been more closely examined, finding the average annual cost of hospitalisation for extremely preterm babies in the first year of life alone is more than $180,000.[5]

This How to Treat covers management of the complications of prematurity, system by system. It aims to ensure GPs have a strong understanding of the short- and long-term sequelae of preterm birth and how best to support survivors of preterm birth and their families, to enable the child to achieve their full health and developmental potential.

MANAGEMENT OF PREMATURITY

TABLE 1 list the complications of prematurity and the required follow-up.

Eyes and ears

Retinopathy of prematurity (ROP) increases in incidence and severity with lower gestational age at birth, lower birthweight, duration of mechanical ventilation and oxygen exposure.

It primarily affects infants born at less than 31 weeks and weighing less than 1250g. It is a pathology of abnormal retinal vessel proliferation

in an environment of both hypo- and hyper-oxia within the developing retina (see figures 2, 3 and 4). Untreated, it can lead to retinal detachment and blindness.

Premature infants undergo screening for ROP in the neonatal ICU (NICU) by dilated eye examination, with the majority showing only mild self-limiting disease. However, a small number (approximately 200 a year in Australia) require intervention with laser surgery (retinal photocoagulation), vascular endothelial growth factor (VEGF)-inhibitor injection or both.[3] Progression of ROP can still occur after intraocular injection, requiring laser treatment at a later stage, but injection is sometimes used as a temporising measure if the infant is too unwell for laser.[6] Screening for ROP ceases when the retina is fully vascularised, usually at term corrected age, but many will need follow up beyond that. Fortunately, owing to the judicious use of oxygen, screening and treatment, only a handful of premature Australian babies with ROP, out of hundreds, develop long-term blindness each year.

In addition to ROP, children born prematurely are at increased risk of visual impairment regardless of ROP status and low birthweight, including refractive errors and strabismus.[7] This is because normal ocular development is impacted by development ex utero, as well as contributions from cerebral visual impairment.[7] Consider visual assessment for ex-premature children displaying learning or behavioural difficulties.

Hearing screening is important for all newborns, particularly in those born prematurely, as between 1% and 3% experience hearing loss, depending on degree of prematurity.[3] The causes for this are multifactorial and may include exposure to common ototoxic medication in NICU, such as aminoglycosides; congenital infections; late-onset sepsis; and potentially prolonged exposure to the noise of NICU.[8]

All premature infants should have a hearing screen on discharge (usually conducted by automated auditory brainstem response) and again at 8-12 months if additional risk factors are present. These include degree of prematurity, ventilation for longer than five days, gentamicin for longer than three days, jaundice at exchange transfusion level, significant ▸

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NEED TO KNOW

Extremely premature infants are surviving at a greater rate and from lower gestational ages in Australia.

Prematurity is a condition with multisystem complications in the short and long term.

The most common short-term challenges after discharge home include nasogastric feeding and feeding difficulties, home oxygen and poor growth.

The most common long-term complications are chronic lung disease, developmental delay and disability.

Awareness of the complications of prematurity can aid identification of reversible causes of developmental delay.

Ex-premature infants require screening investigations and assessments in the community after discharge.

Parental distress after a neonatal intensive care admission can be profound and life-changing.

Figure 2. Fundus image of ROP.

Figure 2A. Healthy retina.

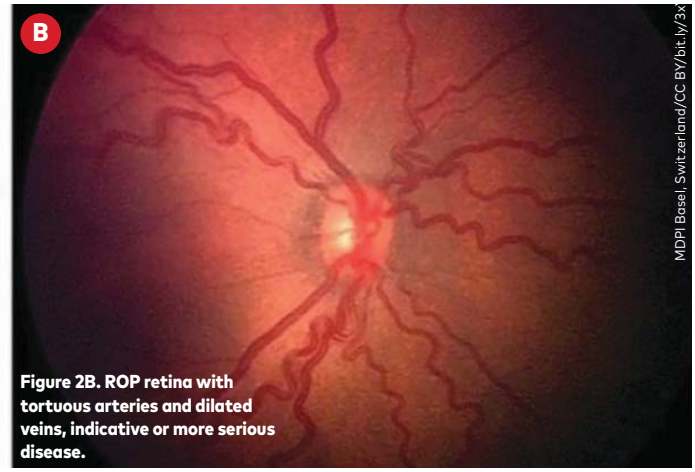

Figure 2B. ROP retina with tortuous arteries and dilated veins, indicative or more serious disease.

◂ infection or a family history of hearing impairment.[9]

If hearing impairment is present on screening, refer to audiology; early detection is useful for planning interventions, such as hearing aids or a cochlear implant.

Prematurity and the developing brain

Children born prematurely have a consistently high rate of developmental delay and neurodisability. The prevalence in survivors of extreme prematurity is highest in the most premature babies — those born at less than 28 weeks.[3,10] These sequelae of preterm brain injury include cerebral palsy; cognitive impairment; visual, language and hearing impairment; and often global functional impairment with a combination of the above.

These occur because of injury and inflammation to the preterm brain, precipitated by intraventricular haemorrhage (IVH, see figure 5), hypoxia, sepsis and exposure to noxious stimuli through long-term hospitalisation.

When ultrasound was the only neuroimaging modality available, intraventricular haemorrhage was thought to be the dominant pathology underpinning these sequelae. However, with increasing use of MRI at term-corrected age, diffuse white-matter injury has been identified as a much more significant contributor, resulting from inflammatory injury to the pre-oligodendrocyte, reducing white-matter volume.[11]

Approximately 20% of infants born at 23-24 weeks experience severe intraventricular haemorrhage, and a proportion of survivors of this condition will develop periventricular leukomalacia, post-haemorrhagic hydrocephalus requiring insertion of a shunt (Rickham reservoir with or without a ventriculoperitoneal shunt) and a high risk of subsequent cerebral palsy.[3] This risk is reduced to less than 2% by 28 weeks, but other complications of prematurity — such as late-onset sepsis or neonatal surgery — represent an ongoing challenge for optimal development of the preterm brain.[3]

Although preterm brain injury represents a leading cause of disability for survivors of prematurity, options for treatment remain limited. Post-haemorrhagic hydrocephalus can be treated with shunt surgery, but the injuries themselves are best treated with prevention. Introduction of broad neuroprotective measures antenatally, including corticosteroids and magnesium sulfate, has been shown to reduce the rate of neurological injury in preterm infants, as has exogenous surfactant, caffeine and attention to judicious and volume-targeted ventilation. Sustained quality-improvement practices with an emphasis on how we handle and position the most premature infants have also demonstrated reduced rates of brain injury in multiple centres.[12,13]

Survivors of extreme prematurity require long-term follow-up of neurodevelopment — in particular, focused assessment to identify those who need early intervention.

Respiratory distress syndrome and bronchopulmonary dysplasia

All extremely premature infants, and most babies born at less than 32 weeks, require respiratory support from birth because of immature lungs and surfactant deficiency.

Most infants born at 22-24 weeks in Australia require mechanical ventilation, as do many at 25-27 weeks.[3] Exogenous surfactant, available since the 1990s, has greatly improved survival and limited the severity of lung disease for premature infants. The use of mechanical ventilation in the NICU has declined after CPAP was shown to be non-inferior to intubation and reduced the need for oxygen at 28 days.[14]

Bronchopulmonary dysplasia (BPD, see figure 6), also known as neonatal chronic lung disease, is a pathology of abnormal lung development caused by a disturbance of normal lung growth during the saccular stage of lung development, resulting in chronic respiratory insufficiency. There have been various definitions of the disease, but the current definition most widely used in Australia is the need for any respiratory support at 36 weeks postmenstrual age (gestational age at birth plus chronological age since birth).[15]

BPD is diagnosed in 80% of babies born at 24 weeks, falling to fewer than 40% by 28 weeks.[3] It is a condition requiring prolonged respiratory support, often well post-term, and the most severe cases may require positive-pressure support at home and tracheostomy.

It is associated with adverse neurological outcomes compared with premature infants without BPD, and its treatment, such as respiratory support, interferes with normal development at a time when babies are supposed to be learning to feed and interact with their carers. Despite the reduced use of mechanical ventilation in the PAGE 22 ▶

◀ PAGE 20 post-surfactant and CPAP era, this has not seemingly reduced the incidence of BPD at 36 weeks or lung function later in childhood for survivors.[16]

Secondary pulmonary hypertension related to BPD is a significant concern for babies with the most severe BPD and results in the need for prolonged ventilation and medical management with agents such as inhaled nitric oxide and sildenafil.[17]

Infants with BPD require a screening echocardiogram to look for pulmonary hypertension; this is a significant risk factor for adverse long-term outcomes.[18]

Many infants will still require oxygen on their due date and thus go home on oxygen; these are mostly babies born at 23-25 weeks. This requires the support of a paediatric respiratory team and home oxygen service.

In addition to oxygen support, babies on home oxygen are at higher risk of morbidity with common respiratory infections; therefore, respiratory syncytial virus (RSV) prophylaxis with palivizumab is recommended.[19]

Cardiac complications of extreme prematurity

While structural congenital heart disease is more common in the preterm population than term infants, it is not a cause of major morbidity in this group. Babies born extremely prematurely commonly have patent ductus arteriosus (PDA, see figure 7); this results in pulmonary over-circulation and volume loading of the left ventricle and sometimes congestive cardiac failure.

In most cases, PDA is treated medically with ibuprofen, indomethacin or paracetamol, which act to close or reduce the size of the PDA. Many will ultimately close spontaneously over time. In a few infants, surgical ligation is required; this is performed via thoracotomy, although transcatheter devices have been introduced in some centres overseas.[20]

Long-term data are emerging that link prematurity with long-term cardiovascular risk, including hypertension, ischaemic heart disease and

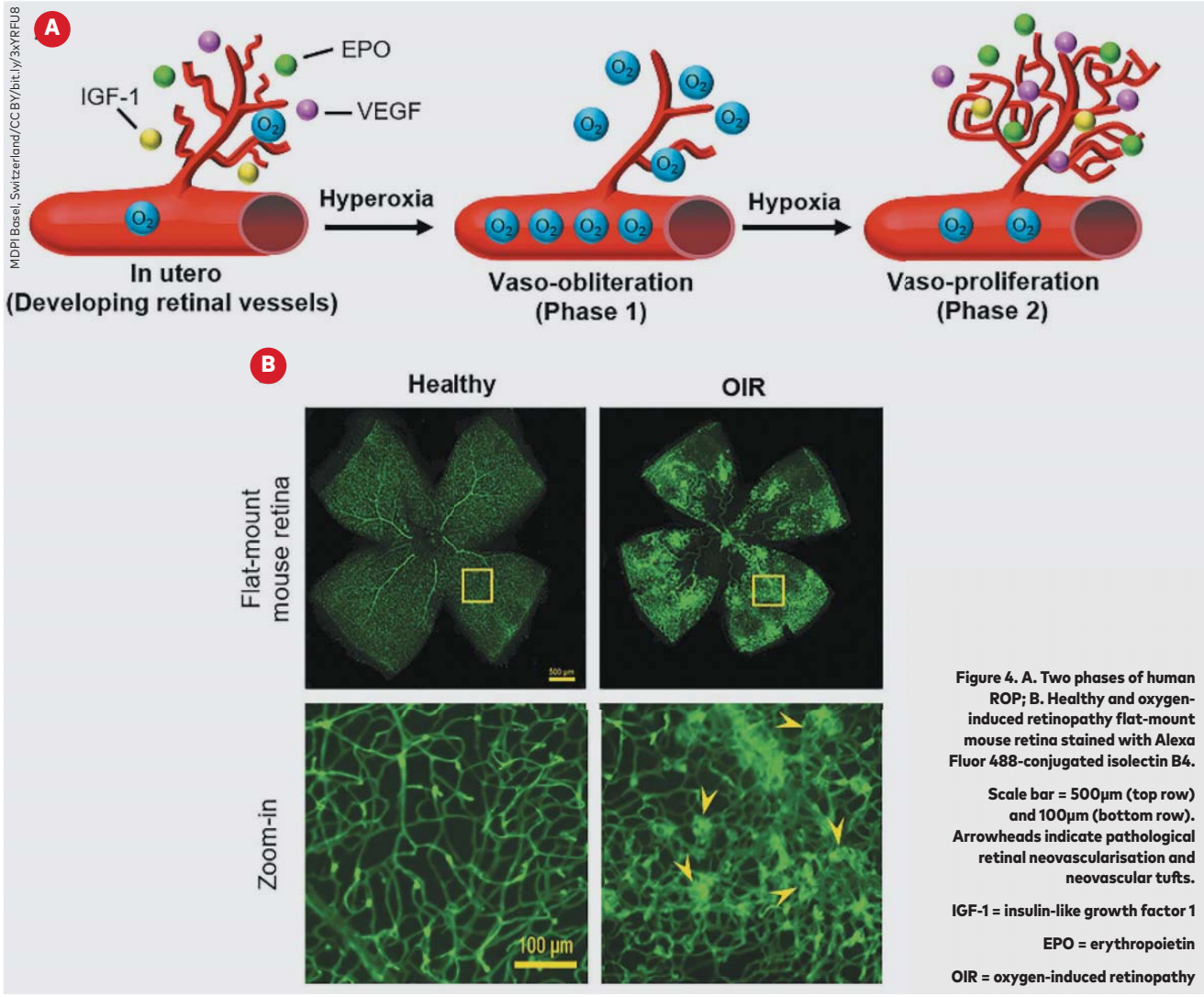

Figure 4. A. Two phases of human ROP; B. Healthy and oxygen-induced retinopathy flat-mount mouse retina stained with Alexa Fluor 488-conjugated isolectin B4.

Scale bar = 500µm (top row) and 100µm (bottom row). Arrowheads indicate pathological retinal neovascularisation and neovascular tufts.

IGF-1 = insulin-like growth factor 1

EPO = erythropoietin

OIR = oxygen-induced retinopathy

cardiac failure in adult life.[21] The mechanisms for this are not fully understood and likely relate to abnormal vascular development and cardiac remodelling in these infants. Consider early lifestyle and blood-pressure screening for adults born at less than 28 weeks.

Gastrointestinal complications

Gastrointestinal issues of the premature newborn broadly encompass surgical pathologies and feeding difficulties. One of the greatest threats to very preterm babies is necrotising enterocolitis (NEC, see figure 8). This complex pathology — caused by an interplay of inflammation, ischaemia and infection in the preterm intestine — can lead to severe complications, including short-gut syndrome and death. Roughly 7% of babies born at less than 28 weeks develop NEC; this falls to fewer than 2% for more mature babies born between 28 and 32 weeks.[3] The most consistently associated risk factors are low birthweight and gestational age at birth, as well as haemodynamic instability and intrauterine growth restriction.[22]

Another relatively common entity is spontaneous intestinal perforation in extremely preterm infants. This is not usually associated with the systemic inflammation of NEC but is still treated with a laparotomy and stoma formation, resulting in prolonged parenteral nutrition.

For the surgical infants who develop short-gut syndrome, and even those without, the NICU course is often characterised by prolonged periods of parenteral nutrition, long-term venous access and its associated risks, and delayed enteral and oral feeding. These infants require multidisciplinary follow-up on discharge, including paediatric PAGE 24 ▶

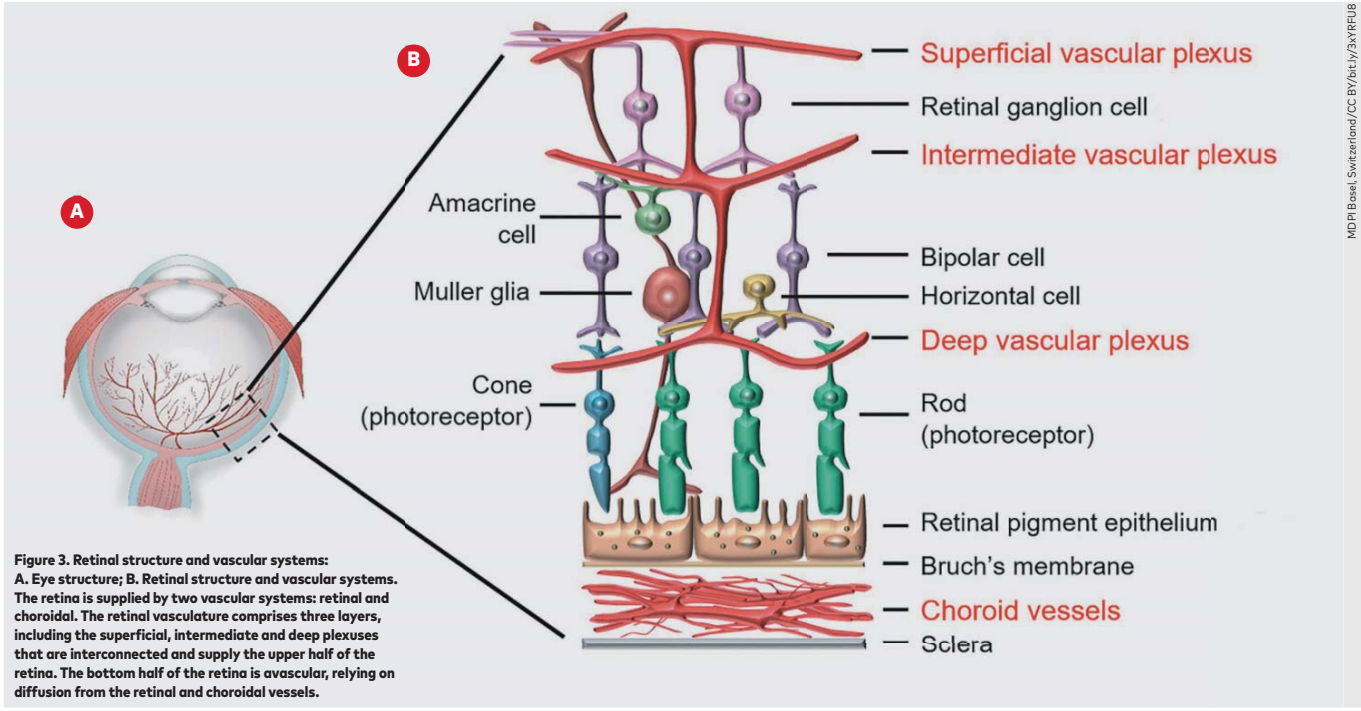

Figure 3. Retinal structure and vascular systems: A. Eye structure; B. Retinal structure and vascular systems. The retina is supplied by two vascular systems: retinal and choroidal. The retinal vasculature comprises three layers, including the superficial, intermediate and deep plexuses that are interconnected and supply the upper half of the retina. The bottom half of the retina is avascular, relying on diffusion from the retinal and choroidal vessels.

◂PAGE 22 gastroenterologists and dietitians.

A more common issue facing ex-premature infants is delay in oral feeding. Infants born extremely prematurely, especially the most premature and those who have experienced brain injury, will often require nasogastric feeding beyond term-corrected age. Ideally, this involves a multidisciplinary team, including speech pathology, parental education and close follow-up with a home enteral feeding program.

Many of these babies will go on to full oral feeds in due course, but others do not, and this may necessitate gastrostomy insertion. Inability to achieve full oral feeds can be a result of underlying neurological status, oral aversion because of prolonged hospitalisation or a combination of both factors.

Kidneys and bones

Infants born very prematurely have immature renal tubules, very large surface-area-to-body ratios and challenging fluid management in the first few days to week of life. Those born at 22-24 weeks can lose more than 40mL/kg/day via their skin alone; combined with reduced reabsorption in the renal tubules, they can have excessive urine output, needing a total fluid intake of 200mL/kg/day to achieve a neutral fluid balance and avoid hypernatraemia.

In addition to these early challenges, preterm infants are at increased risk of chronic kidney disease later in life. This is due to interruption of normal kidney development, exposure to nephrotoxins and episodes of acute or subacute kidney injury during their NICU stay. Sixty per cent of nephrons are formed in the third trimester of gestation. If a baby is born at 24 weeks, this period is disrupted, and the infant is exposed to conditions such as hypoxia, aminoglycosides and hypotension, with subsequent kidney injury. As a result, ex-preterm infants have a two-fold risk of developing chronic kidney disease later in life compared with babies born at term.[23]

Like the bulk of nephrons growing in the third trimester, most fetal acquisition of calcium, iron and phosphate also occurs during that time. This is not surprising given the average 28-weeker

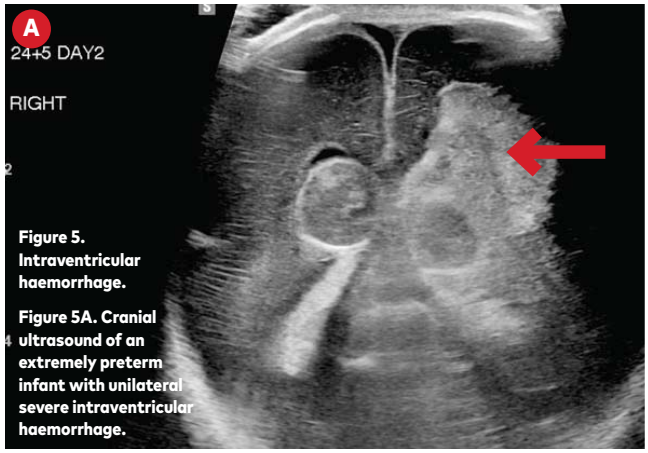

Figure 5. Intraventricular haemorrhage.

Figure 5A. Cranial ultrasound of an extremely preterm infant with unilateral severe intraventricular haemorrhage.

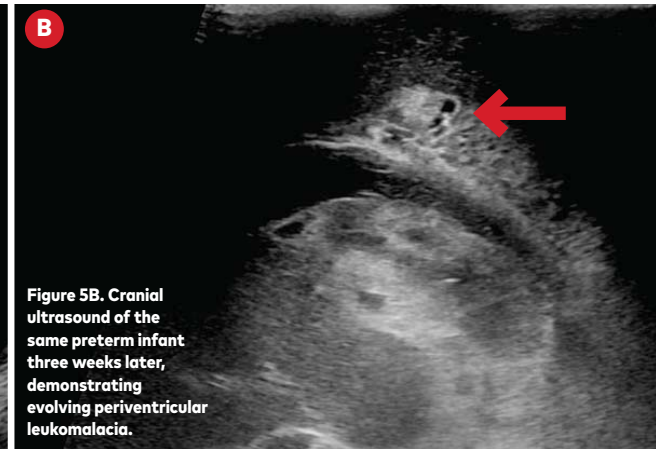

Figure 5B. Cranial ultrasound of the same preterm infant three weeks later, demonstrating evolving periventricular leukomalacia.

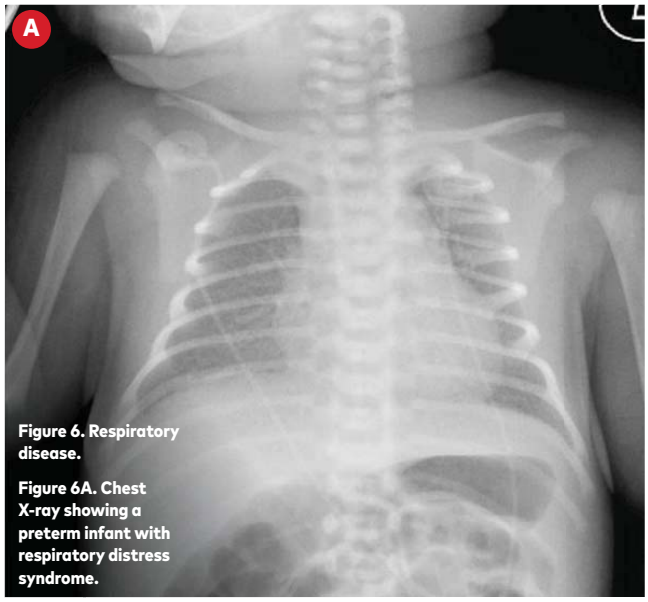

Figure 6. Respiratory disease.

Figure 6A. Chest X-ray showing a preterm infant with respiratory distress syndrome.

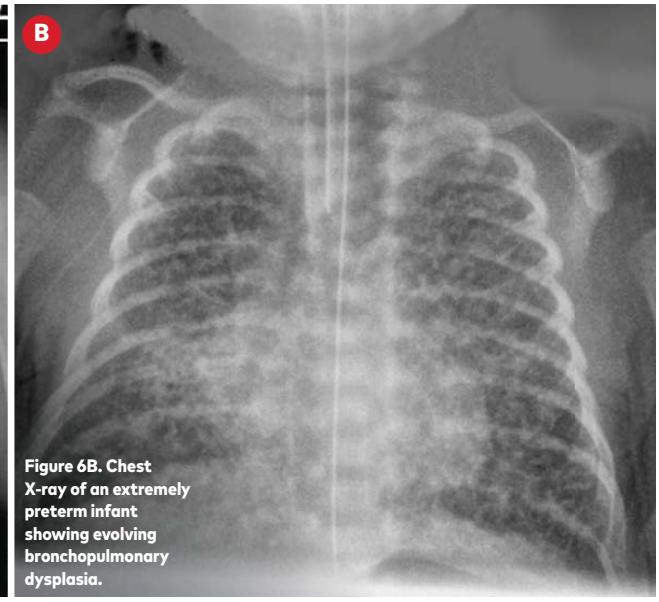

Figure 6B. Chest X-ray of an extremely preterm infant showing evolving bronchopulmonary dysplasia.

is 1kg and is expected to triple in size to 3kg in just 12 weeks. If born extremely prematurely, this period of nutrition is no longer supported by the placenta, and these preterm neonates have very high nutritional and metabolic demands – comparable to an Olympic swimmer at the peak of their training.

These high nutritional needs are met with parenteral nutrition initially, followed by fortified breastmilk or artificial formula feeds. However, because of periods of instability, and sometimes intolerance of supplementation, many preterm infants fall behind with their nutritional requirements. This can lead to metabolic bone disease of prematurity – a disease of high bone turnover, phosphate and calcium deficiency, and subsequent osteopenia (see figure 9). If severe, it can cause pathological fractures akin to those seen in the elderly with osteoporosis.

Metabolic bone disease is treated with oral supplementation with phosphate, calcium, vitamin D and, in rare cases, bisphosphonates. These supplements are often continued beyond term-corrected age, with outpatient monitoring of serum chemistry, while vitamin D is continued until one year of age.

Anaemia of prematurity is also very common because of a combination of iatrogenic anaemia with sampling, inadequate iron stores and a premature bone marrow not able to keep up with erythropoiesis. Almost all infants (90%) born at less than 1000g will require transfusion in the first two weeks, often multiple times. Sampling can be very problematic proportionate to size – for example, a 500g baby has a circulating volume of only around 40mL (80ml/kg). If NICU blood sampling is at 2mL a day, it takes just five days for the baby to lose 25% of their circulating volume. Premature NICU babies are started on enteral iron supplements after a few weeks, and transfusion requirement reduces after establishment of full enteral feeds and improved red-cell production.

PREMATURITY AND THE IMPACT ON FAMILIES

HAVING a sick premature baby is a traumatic experience for parents and

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Figure 1. An intubated female infant born extremely preterm at 26 weeks and six days' gestation, weighing 990g. Photo taken approximately 24 hours after birth.

Table 1. Complications of prematurity and follow-up

System	Complications	Follow-up
Eyes	ROP Higher risk of refractive errors Visual impairment	ROP screening until term Visual assessment at 8-12 months Visual assessment if childhood developmental concerns
Ears	Sensorineural hearing loss	Newborn hearing screen Repeat audiology at 8-12 months Audiology if childhood developmental concerns
Brain	Intraventricular haemorrhage White-matter injury of prematurity Neurodevelopmental impairment	Cranial ultrasound screening until day 42 MRI brain at term-corrected age if high risk* Multidisciplinary follow-up if high risk*
Heart	Patent ductus arteriosus Systemic hypertension Pulmonary hypertension	Screening echocardiography if bronchopulmonary dysplasia at 36 weeks Check blood pressure in adolescence/young adulthood for ex–extremely premature infants
Lungs	Bronchopulmonary dysplasia	Palivizumab prophylaxis against RSV if on home oxygen Importance of routine immunisation schedule, including pneumococcal and influenza vaccination
Kidneys	Acute kidney injury Salt wasting Chronic kidney disease	Higher risk of chronic kidney disease in adulthood
Gastrointestinal	Necrotising enterocolitis Spontaneous intestinal perforation Growth failure Short-gut syndrome Oral aversion	Speech and dietetics referral if poor feeding May need feed fortification
Bones	Metabolic bone disease of prematurity	Phosphate supplementation in early infancy if metabolic bone disease present Vitamin D supplementation until one year of age Iron supplementation

*Born at less than 28 weeks or additional risk factors for brain injury

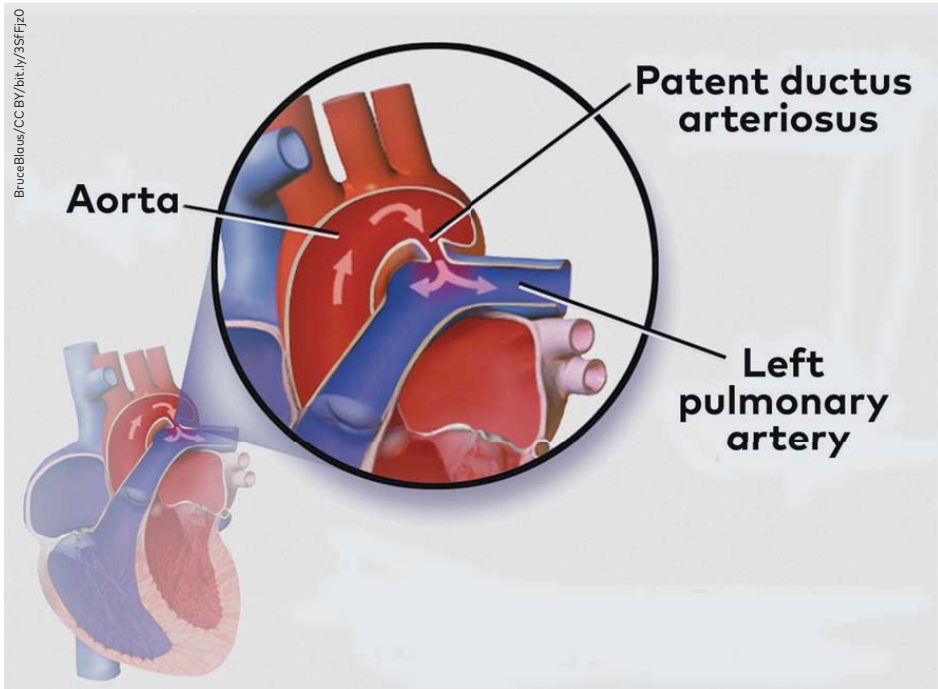


Figure 7. Blood flow with patent ductus arteriosus.

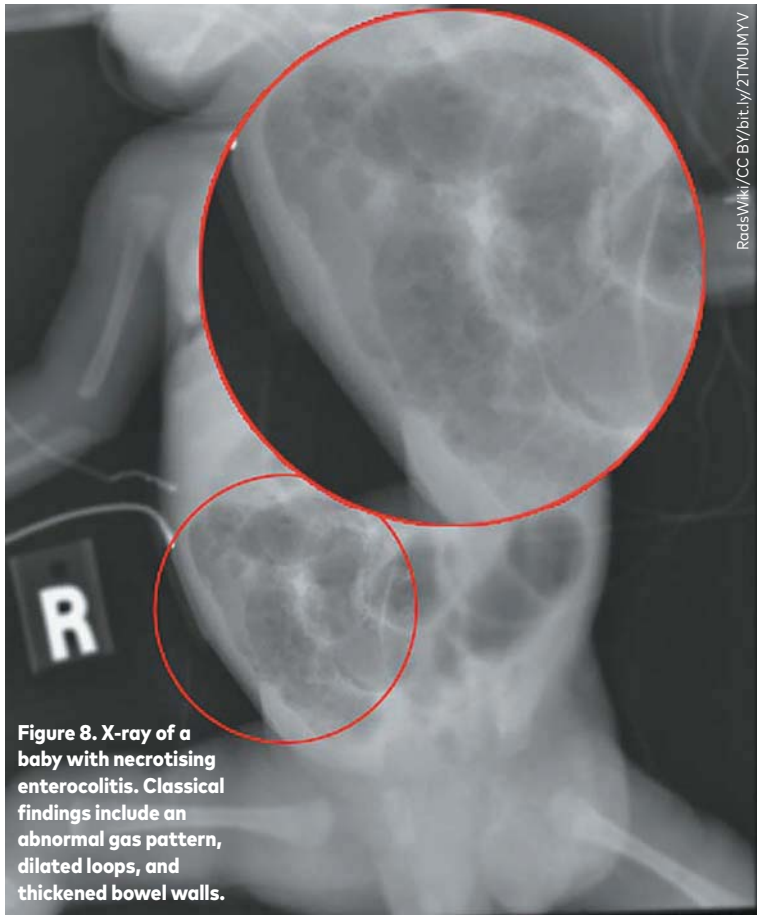


Figure 8. X-ray of a baby with necrotising enterocolitis. Classical findings include an abnormal gas pattern, dilated loops, and thickened bowel walls.

can have lifelong psychological impacts – whether the NICU stay is brief or very long.

Some NICU babies stay in hospital for longer than six months (going home after one year is not unheard of), with associated severe disruption to parents' lives. Parents of NICU babies report feelings of loss, helplessness, lack of control and inability to bond with their baby. And this can persist even when everything is going well.[24]

The NICU experience is very different from what most people expect, with periods of repeated stress and trauma. Estimates of post-traumatic stress in parents of NICU graduates are around 40% – even after one year.[25] Then once their baby is ready to go home, the parents have to care for the infant against the background of that long journey, with many transitioning from highly medicalised and supported scenarios to being relatively isolated at home. In addition, ex-premature infants and those with complex medical needs experience a higher rate of non-accidental injury.[26]

Beyond the psychological stresses of prolonged hospitalisation, families with extremely premature infants in hospital often face unexpected financial challenges. There can be tension between the need to return to work and the guilt associated with not being available for the support of a partner and new family member. These financial pressures are recognised, and advocacy is increasing for improved financial support for parents of high-risk infants.[27]

These risks are mitigated through family integrated care, social work support for families and attempts to allow as much bonding as possible, such as kangaroo care and involving parents in NICU caregiving. However, this is not always possible or optimised, and there is a long way to go in improving parents' experiences in NICU.

COMMON CHALLENGES FACING PREMATURE INFANTS POST-DISCHARGE

COMMON immediate management issues after discharge of preterm infants are home oxygen and nasogastric tube feeding. These are managed by multidisciplinary teams, and the families should be linked with these services and have points of contact for troubleshooting. Parents are taught how to administer nasogastric tube feeds and change the tubes but

may still encounter difficulties; this is a common cause for re-presentation to the GP or ED post-discharge.

Home oxygen is managed by paediatric respiratory services, and education is provided for carers, including use of cylinders, concentrators and requirement of monitoring depending on degree of home respiratory support. Some infants go home on higher levels of support, such as home high-flow nasal cannulae, and have associated higher levels of home nursing care via a specialised home ventilation service.

Feeding difficulties are very common post-discharge; with usual reasons for re-presentation being poor weight gain, jaundice, reflux and constipation.[28]

Ex-preterm infants are often fed with a combination of breastmilk and formula, as well as fortification because of poor weight gain or higher metabolic demand – for example, a baby with BPD on home oxygen. These infants

should gain approximately 15-20g/kg/day. Reflux is more common in premature infants and is often treated with omeprazole, although the use of PPIs for GORD in neonates is not universally recommended.

Consider non-pharmacological strategies, such as positioning, more frequent feeds and thickener. Constipation is a common presentation, particularly in formula-fed infants, and docusate sodium drops can be trialled.

COMMON LONG-TERM CHALLENGES

AS mentioned, developmental disability is common in babies born very prematurely, and this can present as neurobehavioral challenges in early childhood and at school age.

Prematurity has been associated with an increased risk of both autism spectrum disorder and ADHD in childhood.[29,30]

These presentations vary and may include delayed speech and language development, difficulty with emotional regulation, difficulty with social interaction or learning difficulty. When this occurs, it is important to exclude visual or hearing impairment, as well as any underlying reversible organic pathology, such as iron deficiency, hypothyroidism or obstructive sleep apnoea.

Cognitive delay or intellectual disability may also be contributing to these presentations, and the childcare centre or school can be a useful resource in requesting a cognitive and language assessment.

Refer children presenting with these difficulties to a general paediatrician. However, waiting times can be lengthy, and some initial investigations can be very helpful in determining the underlying cause (see box 1).

Free screening tools, such as the NICHD Vanderbilt ADHD scales and Ages and Stages Questionnaire, can be completed by parents and educators before the child sees a paediatrician, which can save time in the assessment of the ex-premature child's presentation.

Formal developmental and cognitive testing can also be provided by child psychologists, but this is usually at significant expense unless conducted in a public clinic, for which there are long waiting lists.

If significant delay is present, it is worth advising parents to call the National Disability Insurance Scheme and register early. This does not require a diagnosis if the child is under seven years old, and with therapy wait times of up to 6-12 months, this process is best started early.

THE FUTURE

IN 1963, President John F Kennedy's prematurely born son died of respiratory distress syndrome after being delivered only a few weeks early; at the time, there were no ventilators suitable for neonates, and exogenous surfactant was not available. For infants born even earlier, fatality was universal. We are now in a situation of ever-improving survival, where even extremely preterm infants born at 23-27 weeks have good chances of survival without moderate-to-severe functional impairment. Much of this improvement since the late 20th century is a result of a few key interventions: antenatal corticosteroids, exogenous surfactant and the development of ventilation appropriate for tiny infants.

A 24-week infant born in Australia now has a 70% chance of surviving, a 10% chance of being diagnosed with cerebral palsy and a 70% chance of survival without moderate-to-severe functional impairment.[3] The limit at which resuscitation is offered to extremely premature infants has continued to fall, where it is now offered routinely at 23 weeks in tertiary centres and even 22 weeks in the absence of adverse risk factors and within the zone of parental discretion.[31]

The challenge lies in continuing to improve survival rates for the most premature babies and reducing the burden of neurodisability among survivors. Ongoing multicentre clinical trials are focusing on interventions, such as inhaled corticosteroids, to reduce the incidence of BPD, as well as improving the often suboptimal nutritional state of premature babies.

Multicentre quality improvement initiatives have shown sustained improvement in outcomes – good examples include the EPIC project in the Canadian Neonatal Network and neonatal 'baby brain bundles' to reduce incidence of intraventricular haemorrhage.[12,13,32] These bundles include interventions such as delayed cord clamping, midline nursing of the

infant head, minimal handling, and standardised ventilation and haemodynamic strategies.[32]

New therapeutics focusing on brain injury and BPD are also under investigation, including stem-cell therapies and immune modulation, with the hope of reducing the inflammatory cascade induced by extreme prematurity and its associated medical interventions.

Beyond immediate medical interventions, models of care are changing, with increasing focus on family-integrated care from the start of the NICU journey. A recent groundbreaking study demonstrated an integrated mother-baby ICU was possible and resulted in improved outcomes, where mothers and premature babies were cared for side by side.[33]

To improve long-term outcomes, early intervention for premature infants showing developmental delay is crucial – this involves early access to services, increased funding and strong social support for parents caring for ex-premature infants.

CASE STUDIES

Case study one

SAM is born at 23^{+1} weeks in the context of spontaneous preterm labour. His mother received two doses of antenatal betamethasone and magnesium sulfate before delivery. Despite attempts to slow contractions, labour progressed.

He has a birthweight of 513g (figure 10).

Sam receives surfactant in the delivery room via endotracheal tube and is admitted to NICU for ventilation. The critical first 72 hours go relatively well: he has umbilical venous and arterial catheters placed and requires only moderate levels of oxygen and brief inotropic support. He receives medical treatment for a patent ductus arteriosus with ibuprofen and is started on enteral feeds on day one.

Serial cranial ultrasounds demonstrate a unilateral grade 2 intraventricular haemorrhage, with no associated ventriculomegaly.

He is extubated to CPAP on day seven; however, he is reintubated two days later, resulting in respiratory decompensation, escalating oxygen requirements and high frequency oscillatory ventilation. Because of his high oxygen requirement and ventilator dependence, Sam is started on systemic dexamethasone to wean his ventilation, and he is PAGE 27 ▶

◀ PAGE 25 successfully extubated for the second time on day 17. He continues to feed and grow on CPAP for several more weeks but experiences another seven-day period of invasive ventilation because of late-onset *Escherichia coli* sepsis on day 45 – fortunately without meningitis. He is weaned from CPAP to high-flow nasal cannulae by 35 weeks corrected age and is still oxygen dependent on his due date. He requires laser surgery for stage 3 retinopathy of prematurity at 38 weeks corrected age.

Sam eventually goes home at 44 weeks, requiring home oxygen but taking full suck feeds. Ongoing medications include phosphate, calcium, vitamin D, omeprazole. He also requires palivizumab for the RSV season. Follow-up includes his local GP, maternal and child health nurse, neonatology, respiratory, ophthalmology and, in the longer term, developmental paediatricians.

Case study two

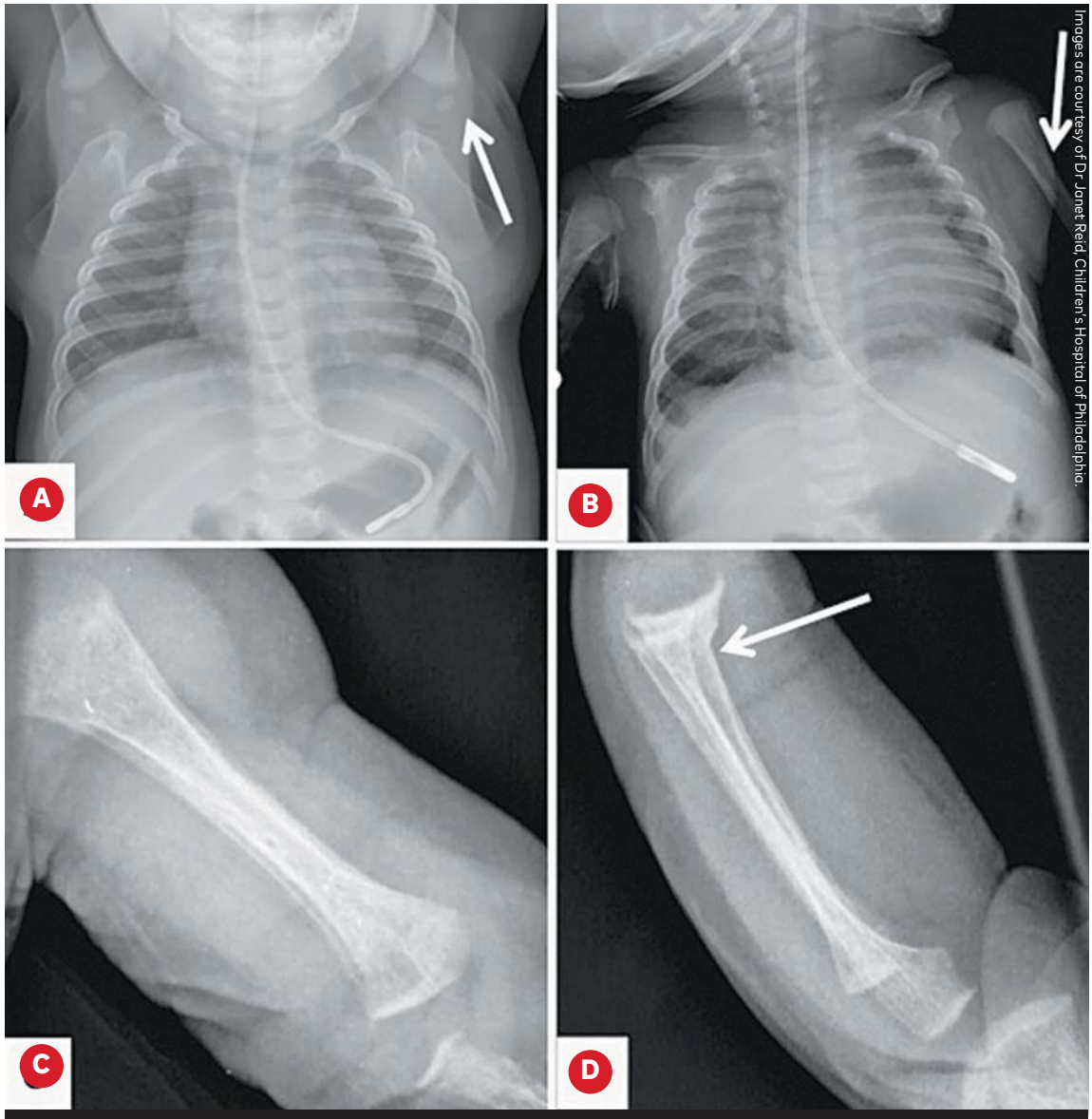
Rosie is born at 24 weeks in the context of placental abruption. Her NICU course is complicated by a grade 4 intraventricular haemorrhage on the left and grade two on the right. She develops progressive hydrocephalus, requires insertion of a Rickham reservoir at age four weeks and subsequent ventriculoperitoneal shunt at 42 weeks corrected age.

She goes home shortly after on full suck feeds and no respiratory support, with follow-up planned with the neonatologists, neurosurgeons, GP and maternal and child health nurse.

Four weeks post-discharge, her parents bring Rosie to the GP because she is slowing down with her feeds and has gained only 10g in the past

Box 1. Suggested initial investigations for an ex-premature infant presenting with early childhood developmental delay

- Laboratory tests:
  - FBC.
  - EUC.
  - Calcium, magnesium, phosphate.
  - Ferritin.
  - B12, folate.
  - Thyroid function tests.
  - Vitamin D.
- Assessments:
  - Audiology.
  - Visual assessment.
- Collateral information:
  - Childcare.
  - School.
  - Ages and Stages Questionnaire.



Images are courtesy of Dr Janet Reid, Children's Hospital of Philadelphia.

Figure 9. X-rays in metabolic bone disease of prematurity.

A. Normal mineralisation of the proximal humerus in a six-month-old former full-term infant; growth-plate formation is shown (arrow).

B. Early demineralisation in the humerus of a six-month-old former extremely low birthweight preterm infant with periosteal reaction (arrow).

C and D. Severe demineralisation with features of rickets, including cupping and fraying of metaphyses, healing fracture (arrow) and cortical thinning.

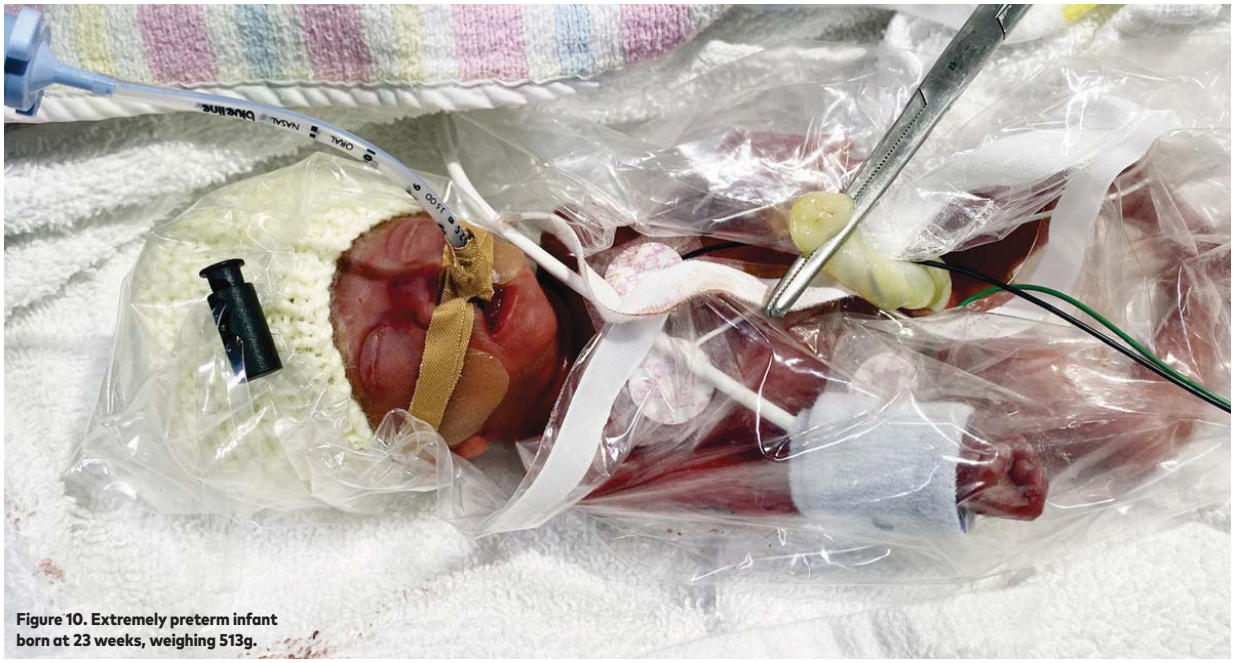


Figure 10. Extremely preterm infant born at 23 weeks, weighing 513g.

week. Her weight has crossed downwards from the 25th to the third centiles for corrected age. She is not vomiting, has no signs of infection, and normal stools, but her parents note she is taking longer to drink bottles and is less interested in feeds than at the time of discharge.

Her GP refers Rosie to the discharge hospital for further assessment, and she is admitted because of weight loss and poor oral feeding. On admission, she is noted to be very irritable on handling, and further investigation reveals rib fractures and retinal haemorrhages.

A referral is made to child protection, and further investigations reveal a situation of severe home stress and domestic violence that has escalated since Rosie came home.

Case study three

Azri is born at 27 weeks in the context of pre-eclampsia and severe fetal growth restriction, with a birthweight of 490g. She has a long and complicated NICU stay but eventually goes home at 47 weeks corrected age on full oral feeds and no respiratory support. Follow-up until age two shows delayed motor and language milestones, but only by about three months, and she is discharged from hospital outpatients.

Azri, now aged four, is brought to the GP as her parents are concerned about a lack of speech development and very fussy eating. She is using a few short sentences but mostly single words. She refuses most food except toast, but her weight is tracking appropriately along her centile for age. They describe frequent "meltdowns" if she must share with others at kindergarten, and they say their older term-born child was not like this. They ask, "Is this related to her prematurity?"

Azri undergoes audiology, revealing mild sensorineural hearing loss bilaterally – potentially related to her long NICU stay and aminoglycoside exposure. She also has a low ferritin and haemoglobin that is likely related to her restricted diet. Her GP starts her on iron supplements and refers her to a general paediatrician.

Azri undergoes a multidisciplinary assessment, including cognitive and language assessments, and is diagnosed with autism spectrum disorder.

CONCLUSION

ADVANCES in perinatal care have achieved steady improvements in survival for infants born prematurely, with most now surviving even if born extremely prematurely at less than

28 weeks. However, many survivors of prematurity experience a significant burden of chronic medical and developmental sequelae of preterm birth well into childhood and adult life.

While the most extremely premature infants are likely to have multidisciplinary team involvement following discharge from NICU, this is not the case for all, and the first point of contact for these infants and their families will likely be their GP.

GPs play a vital role in the ongoing care and support of these infants, and a systems-based approach can be useful in assessing for complications of prematurity and organising appropriate screening investigations and referrals.

A head-to-toe assessment of the child's wellbeing in the context of the prematurity complications described here, together with their family and social circumstances, forms the framework for ongoing assessment and referrals for these patients.

FURTHER READING

- ***Aust J Gen Pract* 2019; Jan-Feb:** bit.ly/3P8oyE2
- **Am Fam Physician 2007; 15 Oct:** bit.ly/3PeAm7N
- **Ages and Stages Questionnaire:** bit.ly/3AY3zzP
- **NICHD Vanderbilt ADHD Scales:** bit.ly/3RCcFIF

References

Available on request from howtotreat@adg.com.au

How to Treat Quiz.

PREMATURITY

GO ONLINE TO COMPLETE THE QUIZ **ausdoc.com.au/how-to-treat**

1. **Which THREE statements regarding prematurity are correct?**
   - **a** It is the second largest cause of mortality and morbidity for newborn infants.
   - **b** The most common cause of prematurity is elective delivery for pathologies.
   - **c** Most preterm infants are born between 32 and 36 completed weeks of gestation.
   - **d** Premature infants have a significant risk of neurodevelopmental sequelae.

2. **Which ONE is NOT a risk factor for retinopathy of prematurity?**
   - **a** Lower gestational age at birth and lower birthweight.
   - **b** Aminoglycoside exposure.
   - **c** Duration of mechanical ventilation.
   - **d** Oxygen exposure.

3. **Which THREE are causes of developmental delay and neuro-disability in premature babies?**
   - **a** Intraventricular haemorrhage.
   - **b** Hypoxia.
   - **c** Anaemia of prematurity.
   - **d** Sepsis.

4. **Which TWO statements regarding bronchopulmonary dysplasia are correct?**
   - **a** Mechanical ventilation results in better outcomes compared with CPAP in NICU.
   - **b** Exogenous surfactant has greatly improved survival and limited the severity of lung disease for premature infants.
   - **c** BPD does not result in adverse neurological outcomes.
   - **d** Babies on home oxygen require RSV prophylaxis.

5. **Which THREE statements regarding the cardiac complications of prematurity are correct?**
   - **a** Structural congenital heart disease is more common in the preterm population than term infants.
   - **b** Structural congenital heart disease is a cause of major morbidity of preterm infants.
   - **c** Babies born extremely prematurely commonly experience a patent ductus arteriosus.
   - **d** Prematurity has been linked to long-term cardiovascular risk.

6. **Which ONE is the most common gastrointestinal complication in premature infants?**
   - **a** Necrotising enterocolitis.
   - **b** Delay in oral feeding.
   - **c** Spontaneous intestinal perforation.
   - **d** Short-gut syndrome.

7. **Which TWO statements regarding kidneys and bones in premature infants are correct?**
   - **a** Preterm infants are at increased risk of chronic kidney disease later in life.
   - **b** Premature babies require vitamin D, iron and phosphate supplementation until the age of one.
   - **c** Transfusion is seldom required in infants less than 1000g at birth.
   - **d** Metabolic bone disease of prematurity may cause osteopenia and pathological fractures.

8. **Which THREE statements regarding premature babies are correct?**
   - **a** Ex-premature infants experience a higher rate of non-accidental injury.
   - **b** Families may experience relationship breakdown and financial stress.
   - **c** Prematurity is associated with an increased risk of autism spectrum disorder and ADHD in childhood.
   - **d** Refer children presenting with cognitive delay or intellectual disability to a psychologist.

9. **Which THREE are common feeding issues post-discharge of a premature baby?**
   - **a** Constipation.
   - **b** Poor weight gain.
   - **c** Colic.
   - **d** Reflux.

10. **Which THREE are the most common long-term complications of prematurity?**
    - **a** Cognitive impairment.
    - **b** Chronic lung disease
    - **c** Developmental delay.
    - **d** Disability.

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- Each article has been allocated 2 RACGP CPD points and 1 ACRRM point.
- RACGP points are uploaded every six weeks and ACRRM points quarterly.