

Fanaroff and Martin's

NEONATAL-PERINATAL MEDICINE

Diseases of the Fetus and Infant

TWELFTH EDITION

Richard J. Martin, MBBS, FRACP

Professor, Pediatrics, Reproductive Biology, and Physiology and Biophysics
Case Western Reserve University School of Medicine
Drusinsky/Fanaroff Chair in Neonatology
Rainbow Babies and Children's Hospital
Cleveland, Ohio

Avroy A. Fanaroff, MD, FRCPE, FRCPC

Emeritus Professor, Pediatrics and Reproductive Biology
Case Western Reserve University School of Medicine
Emeritus Eliza Henry Barnes Chair in Neonatology
Rainbow Babies and Children's Hospital
Cleveland, Ohio

Associate Editor

Michele C. Walsh, MD, MSE



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large mass on the fetal cardiovascular system. The most frequently used approach is a debulking resection via maternal laparotomy and open hysterotomy (Fig. 12.4). Minimally invasive techniques are also described and include both interstitial ablation and vascular interruption techniques with radiofrequency or laser energy sources. A systematic review of case reports of both open and minimally invasive interventions for SCT in the setting of nonimmune hydrops found a survival of 55% (6/11) after open hysterotomy and SCT debulking, compared with 30% (6/20) after minimally invasive interventions, including radiofrequency and laser ablation.⁴⁰ However, given reporting bias, survival is likely to be over-represented in these series, making a true comparison of open and minimally invasive techniques difficult. In addition, although survival rates were poor in both cohorts, these interventions were performed in fetuses in the presence of hydrops, which confers a very high risk for fetal demise without intervention. Finally, in both open and minimally invasive cohorts, mean gestational age at delivery was less than 30 weeks, emphasizing the risk for preterm birth after surgical intervention and the need for intensive neonatal care after birth.

Additional experience is needed with minimally invasive techniques before they are abandoned in favor of open resection. Typically, although they are lumped together as “minimally invasive,” there is some suggestion that not all techniques employed are equal. A review sought to compare interstitial ablative procedures and vascular disruption procedures.⁴⁹ Eleven fetuses underwent devascularization procedures, with a survival of 63.6%. This compared favorably with a survival of 40.9% in 22 fetuses who had interstitial ablation. The authors hypothesized that the sudden tumor necrosis and subsequent risk for hemorrhage contributed to decreased survival with interstitial ablation.

Cystic SCTs are usually amenable to percutaneous drainage or shunt placement, which may not be indicated given the favorable prognosis for cystic SCTs and the lower incidence of fetal hydrops with cystic SCTs.⁴⁵ However, immediate decompression of an SCT may be indicated just prior to delivery to prevent dystocia, to



• Fig. 12.4 Open fetal debulking of sacrococcygeal teratoma.

facilitate cesarean delivery, and to prevent rupture with spillage of neoplastic cells.

Fetal Neck Mass

The fetal neck mass poses a significant risk to the fetus, with a risk of mortality that ranges from 10% to 57% and a 20% risk of neurodevelopmental delay caused by hypoxia.⁵⁰ Obstruction of the trachea and esophagus can result in polyhydramnios and preterm labor; local compression can lead to craniofacial defects and cranial nerve injury. Highly vascular lesions can result in high-output cardiac failure with nonimmune fetal hydrops and subsequent intrauterine fetal demise (IUID). The primary histologic lesions encountered are cervical teratoma, cystic hygroma, or other vascular malformations. Rarely, neck masses can include thymic cysts or congenital neuroblastoma.⁵⁰

Fetal neck masses are readily identified on prenatal ultrasound, and upon diagnosis, fetal MRI should be obtained to better characterize the mass—specifically to distinguish between a cystic hygroma and teratoma based on the presence of fat. Fetal MRI can also aid in the identification of the fetal trachea. Ultrasound imaging can help in diagnosis and prognosis by demonstrating polyhydramnios, the lack of a fluid-filled stomach indicating esophageal compression, and a dilated hypopharynx. The tracheoesophageal displacement index (TEDI) is a useful prognostic measurement described by the group at Texas Children’s Hospital.⁵⁰ This measurement is defined as the sum of the lateral and ventral displacement of the trachea and esophagus from the ventral-most aspect of the cervical spine. In their series of 24 prenatally diagnosed neck masses, all patients with a TEDI of greater than 12 mm had a complicated airway, whereas only 46% of those with a TEDI less than 12 mm had a complicated airway. Furthermore, the authors found that the presence of a cervical teratoma or polyhydramnios also increased the risk for a complicated airway.

Pregnancies complicated by a fetal neck mass require very close surveillance. Large masses that cause significant extension of the neck require delivery via cesarean section because of the risk of dystocia. In the presence of fetal hydrops prior to 30 weeks’ gestation, successful open fetal resection has been reported.⁵¹ In all cases, at the time of delivery, immediately securing the airway is paramount because 35% of cases in which the neonate dies immediately are a result of airway compromise. For this reason, the EXIT-to-airway procedure should be considered to permit safe establishment of the airway prior to delivery. However, it is important to keep in mind that most cystic neck masses do not cause airway obstruction, and judicious use of EXIT procedures for these patients is required.

If delivery is pursued via EXIT-to-airway procedure, strict adherence to anesthetic principles is required. General maternal anesthesia is required to maintain complete uterine relaxation and preserve uteroplacental circulation so that the fetus does not undergo premature transition from fetal to neonatal circulation. During an EXIT-to-airway procedure, the uterus is exposed and a hysterotomy is made

to deliver the fetus's head and neck. An extremity is also exposed to permit pulse oximetry and intravenous access if needed. Direct laryngoscopy can be attempted for endotracheal intubation. Airway management can be escalated using bronchoscopy or tracheostomy if laryngoscopy is not successful. In the presence of a large neck mass, the trachea is often deviated, and this displacement must be recognized prior to tracheostomy. In cases of large cystic lesions, decompression of the cyst may facilitate establishing an airway by relieving any airway compression. When an airway still cannot be obtained, resection of the mass while still on uteroplacental circulation may be necessary, converting the procedure to an EXIT-to-resection. Once an airway has been established and confirmed (usually by flexible bronchoscopy), the umbilical cord can be divided and the baby completely delivered.

A systematic review of reported cases of EXIT until 2018 revealed 235 cases performed at a mean gestation of 35.1 weeks.² Fetal and neonatal death occurred in 17% (40/235) of cases. There were 29 adverse fetal events, the most frequent being failure of intubation or tracheostomy, and 13 adverse maternal events, the most common being postpartum hemorrhage. The group at Children's Hospital Los Angeles recently described fetoscopic insertion of an endotracheal tube to secure the fetal airway, which may be a minimally invasive alternative to EXIT.⁵²

Postdelivery and postresection hypothyroidism and hypoparathyroidism are the most common nonairway complications. Therefore an endocrine evaluation should be initiated, with specialist consultation as indicated. Given the small malignant potential for cervical teratomas, screening for recurrence should also be implemented by following alpha-fetoprotein levels and obtaining surveillance imaging. Cystic hygromas and other vascular malformations presenting as fetal neck masses can be difficult to manage postnatally given that these lesions have a propensity for significant cervical, oral, and intrathoracic extension, making complete resection difficult, recurrence rates high, and disfigurement likely.

Myelomeningocele

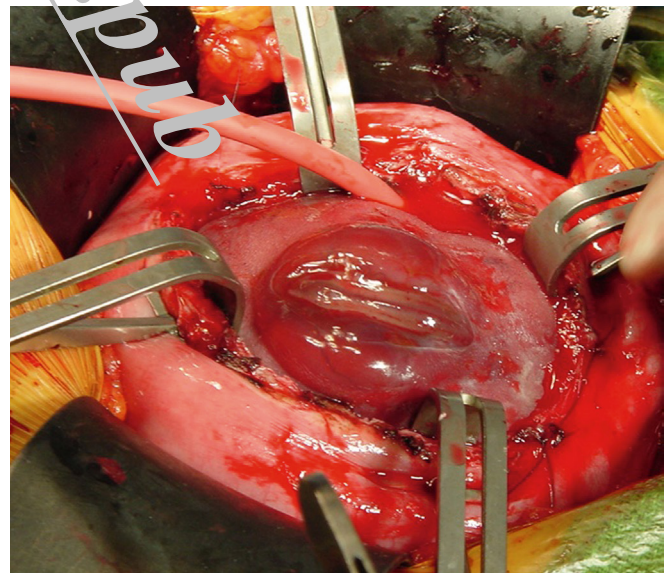
Myelomeningocele (MMC), or spina bifida, is characterized by incomplete closure of the neural tube resulting in exposure of the spinal canal elements. This can occur anywhere along the spine but most commonly occurs at the lumbar or cervical vertebral levels. The primary manifestations include neurologic deficits with motor and somatosensory abnormalities that correspond to the level of the spinal defect, autonomic nervous system injury resulting in impaired bowel and bladder function, and the Chiari II malformation of the hindbrain leading to hydrocephalus and the need for ventriculoperitoneal (VP) shunting. Live-born infants with MMC have a 10% risk of mortality.⁵³ Moreover, MMC confers severe long-term morbidity to the child, including paralysis and bowel and bladder dysfunction. Damage to the spinal cord and peripheral nerves is

usually evident at birth and irreversible despite early postnatal surgical repair.⁵³

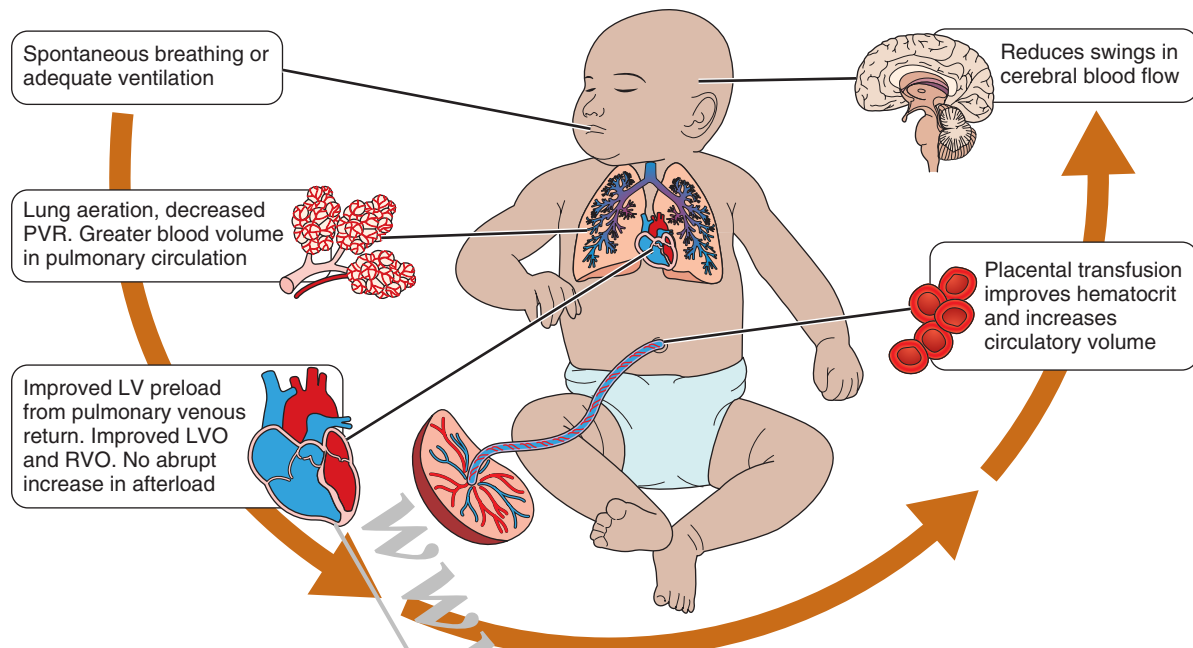
The rationale for fetal intervention in MMC is centered on a "two-hit" hypothesis for development of morbidity, in which the first hit is the original neural tube defect that results in an open spinal canal and the second hit is postulated to be trauma to the exposed neural elements while the fetus is in utero.⁵⁴ By minimizing secondary trauma to the exposed neural elements through fetal repair, it was hypothesized that neurologic outcomes for MMC could be improved.

Open fetal repair of MMC is performed through a maternal laparotomy and open hysterotomy (Fig. 12.5) with either primary repair of the defect or coverage of larger defects using allografts.

Initial success with open surgical repair prompted a multi-institutional prospective randomized trial, known as the Management of Myelomeningocele Study (MOMS), comparing open fetal repair at 19 to 26 weeks' gestation with postnatal repair.⁵³ A power analysis based on the initial, nonrandomized human studies indicated that 200 patients were required to adequately study the primary outcome, which was the need for a VP shunt within the first 12 months of life. However, the study was terminated early after demonstrating superiority of prenatal repair. Patients undergoing fetal repair had decreased need for VP shunt placement (40% compared with 82% in the postnatal repair group) and improved motor function, as 42% of the fetal repair group could walk by 30 months of age, compared with 21% in the postnatal repair group. A follow-up study of the 30-month pediatric outcomes of the full cohort of patients in the MOMS trial confirmed the effectiveness of prenatal versus postnatal repair in terms of cognitive development and motor function outcomes.⁵⁵



• Fig. 12.5 Open fetal myelomeningocele repair. (From Fetal therapy. In: Holcomb GW III, Murphy JP, eds. *Ashcraft's Pediatric Surgery*. 5th ed. St Louis: Elsevier; 2010:125–132.)



• **Fig. 34.1** The benefits of delayed cord clamping. LV, Left ventricular; LVO, left ventricular output; PVR, pulmonary vascular resistance; RVO, right ventricular output.

aerate and pulmonary circulation to be established.²¹ The approach of waiting for lung aeration rather than applying a time-dependent concept for DCC is mainly based on several elegant animal studies data.^{22–24} One study in preterm lambs demonstrated that cord clamping before the establishment of lung aeration reduced cerebral blood flow due to a reduction in left ventricular output. This decrease in flow occurs due to the elimination of the umbilical venous blood flow before the replacement of pulmonary venous return as a source of blood volume to the left ventricle.²¹ In addition, changes in heart rate and systemic blood pressure result from the elimination of the low-resistance placental circulation followed by a reduction in left cardiac output and a subsequent rise in cardiac output when breathing has commenced. All of these factors may contribute to brain injury, particularly in the preterm infant, with an immature myocardium and pressure-passive cerebral circulation.^{22,25,26} Conversely, manual lung aeration and establishment of pulmonary circulation before cord clamping allow for better oxygenation and a slower transition of left ventricular preload from umbilical venous blood flow to pulmonary blood flow, reducing the development of hypoxia and ischemia and avoiding any swings in systemic and cerebral blood flow.²⁷ However, limitations of this model include anesthetic medication and endotracheal intubation, which are not possible in human pregnancies.

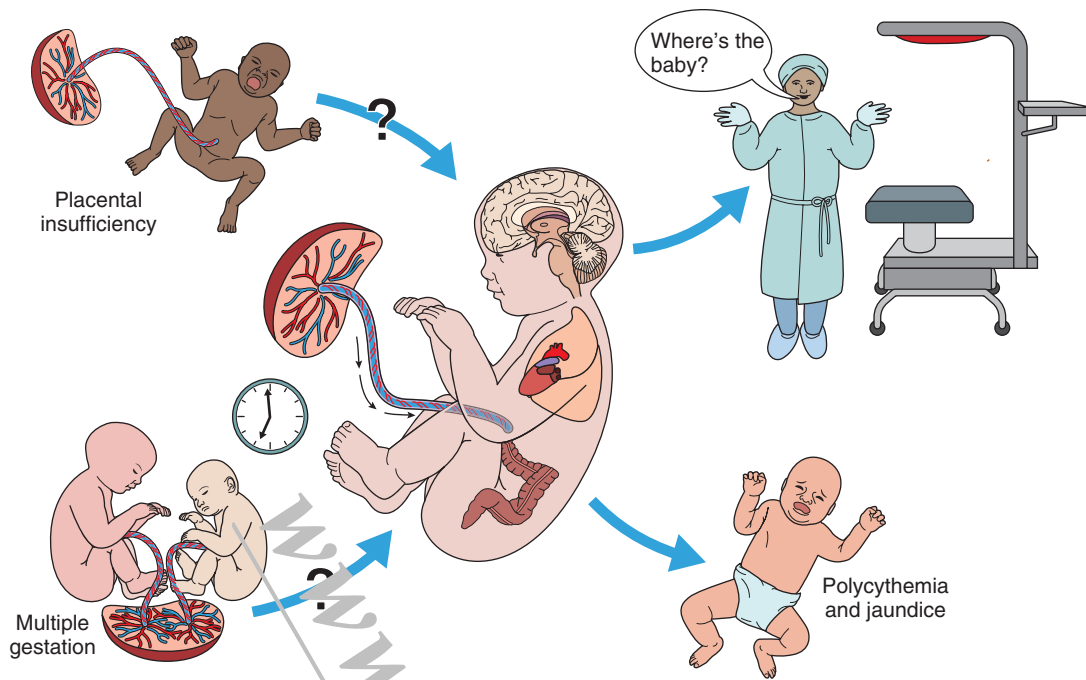
In a randomized controlled trial comparing assisted ventilation with no assisted ventilation during a 60-second delay in cord clamping, there was no significant difference in hematocrit levels or short-term outcomes in 150 preterm infants.²⁸ It is possible that the lack of difference was due to almost all of the infants (around 90%) beginning to breathe by at least 60 seconds with gentle stimulation. Both human and animal

trials have demonstrated that immediately after birth the glottis remains closed, rendering early noninvasive assisted ventilation ineffective.^{29,30} An observational study of 2563 newborns demonstrated that a higher proportion of newborns that were stimulated before cord clamping were more likely to breathe (81.1% vs. 68.9%; $P < .0001$) and needed less bag-mask ventilation (18.0% vs. 32.4%; $P < .0001$). They also had a lower incidence of an Apgar score ≤ 3 at 1 minute (7.6% vs. 11.5%; $P = .001$) and increased odds of spontaneous breathing (adjusted odds ratio = 1.84; 95% confidence interval [CI], 1.48–2.29).³¹ The initiation of spontaneous respiration using stimulation versus actively providing positive pressure ventilation before cord clamping requires further investigation in a randomized controlled trial.

Providing ventilation to a newborn still connected to the umbilical cord has technical challenges. The feasibility of providing resuscitation of preterm infants at the bedside during DCC is possible, but up to 30% of providers in one study had difficulty placing the baby on the resuscitation platform.²⁸ The same group demonstrated the feasibility of providing bedside resuscitation during DCC in term infants, but due to logistical issues they excluded infants born by cesarean delivery.³² Another trial had a similar percentage of infants that required early cord clamping (ECC) due to a short cord.³³ The training of obstetrical and neonatal teams could be time consuming and labor intensive, which may limit the generalizability of this approach until further data is available.

Concerns Related to Delayed Cord Clamping

Although the American College of Obstetricians and Gynecologists (ACOG) recommended DCC in 2010 due to the



• Fig 34.2 Concerns about delayed cord clamping.

reduction of intraventricular hemorrhage (IVH),³⁴ enthusiasm for DCC was tempered by the small numbers of very preterm infants included in these trials and by the concerns of reporting bias.³⁵ A large ($N = 1566$) multicenter trial compared 1 minute of DCC to ICC and did not show significant differences in IVH or other major morbidities.³⁶ The most recent systematic review also did not demonstrate a reduction in any major morbidities, although the mortality was reduced.⁴ In addition, the efficiency of DCC for placental transfusion in cesarean deliveries has been questioned. Prior trials of DCC versus ICC stratified by mode of delivery found no significant improvement in hematocrit levels or tagged red blood cell volume in newborns delivered by cesarean deliveries.^{18,37} ACOG acknowledged that there is still uncertainty as to whether DCC performed during cesarean deliveries can improve placental transfusion.^{38,39}

Another concern with DCC is the potential delay in resuscitation in nonvigorous newborns (Fig. 34.2). Infants that need more resuscitation or are sick at delivery (using Score for Neonatal Acute Physiology [SNAP] or Clinical Risk Index for Babies [CRIB] scores) are more likely to die or have IVH but are currently being excluded from a potentially life-saving intervention.⁴⁰ This has been borne out in research trials, which had significant noncompliance, with up to one-fourth of the subjects randomized to DCC crossing over to ECC.³⁶

A common worry with placental transfusion is “overtransfusion” of blood with DCC. Commonly cited morbidities such as polycythemia or jaundice are cited in both preterm and full-term infants. In a meta-analysis of 15 trials involving 3911 women and term infant pairs, there were no concerns regarding maternal or neonatal outcomes except for the finding of fewer infants in the early clamping group

receiving phototherapy (relative risk [RR] = 0.62; 95% CI, 0.41–0.96).⁴¹ Given the concerns of hyperbilirubinemia, ACOG recommends DCC for term infants if access to treatment for jaundice requiring phototherapy is available.⁸ The increased use of phototherapy with DCC must be weighed against the reduced incidence of iron deficiency and anemia, which may impact the long-term neurodevelopmental outcomes.^{12,14}

In infants with alloimmunization requiring intrauterine transfusion, Garabedian et al.³⁸ found no increase in jaundice with DCC. Pediatric providers must be blinded to the randomization of infants in studies examining jaundice and polycythemia, as beliefs are widespread and do influence practice.³⁷ A systematic review of preterm infants demonstrated an increased incidence of polycythemia (risk difference = 3%, 95% CI, 1–4), and hyperbilirubinemia (mean difference in peak bilirubin +4 mmol/L) in the delayed clamping group compared to the early clamping group. However, there was no difference in partial exchange transfusions for polycythemia or in the exchange transfusions for hyperbilirubinemia.⁴

Infants with placental insufficiency and intrauterine growth restriction (IUGR) have been cited as possible contraindications to DCC due to an inadequate placental transfusion at birth. However, as stated above, the benefits of DCC may be due to both the receipt of placental blood and avoidance of abnormal hemodynamics with ICC. One study of 110 intrauterine growth-restricted infants demonstrated improved measures of systemic blood flow, hematocrit, and ferritin with DCC compared to ECC.⁴² There were also no differences in the rates of polycythemia or duration of phototherapy. Another study of IUGR infants found that DCC was associated with less suspected necrotizing enterocolitis

results but requires additional study. Results of PCR tests showed a broader number of infections, because they not only detect patients with candidemia but are also positive in those with *Candida* peritonitis, candiduria, previous candidal infections, and endotracheal colonization.

BDG levels are helpful if there is uncertainty in deciding need for empiric antifungal therapy and in following response to therapy as levels decrease over time with antifungal therapy. Various cutoff points have been recommended for interpreting BDG levels in neonates. A neonatal study of BDG found higher levels in infants with ICI (364 vs. 89 pg/mL in noninfected neonates), and levels decreased significantly with antifungal therapy to 58 pg/mL (28–81). They suggested the cutoff for BDG be higher (>125 pg/mL) for neonates than adults (>80 pg/mL) because of the effect colonization and other infections (gram-negative and coagulase-negative *Staphylococcus* [CoNS]) can have on BDG levels.²⁸ The BDG levels in infants infected with CoNS were 116 pg/mL (46–128) and 118 pg/mL (52–304) in patients without bacteremia. One challenge is that BDG can be elevated to the same degree with fungal colonization as with ICI, and studies have not critically examined this effect. As several studies have demonstrated, there are high-risk sites that when colonized (e.g., the respiratory tract) may benefit from empiric treatment. One study used endotracheal lavage aspirates with mannan levels ≥ 0.5 ng/mL to decide on pre-emptive treatment and significantly decreased ICI. Further study of pre-emptive treatment at certain BDG levels may be beneficial.

BDG may also give false-positive results following transfusion of blood products in adults and neonates.²⁸ A study of 133 VLBWs found BDG to be higher in transfused (red blood cells or fresh frozen plasma) neonates (170 pg/mL, 65–317) compared to nontransfused infants (57 pg/mL, 34–108; $P < .001$).

Another method that may help with the decision to start early empiric therapy is direct fluorescent assay in buffy coat. This test is a fluorescent stain that binds to structures containing cellulose and chitin. This diagnostic test has been successfully used for identifying hyphae and spores, and results are obtained after only 1 to 2 hours. Other markers of fungal disease being studied include anti-*Candida* antibodies, D-arabinitol (candidal metabolite), and fungal chitin synthase. These markers have some of the same challenges, because they may be present with BSIs, nonblood-stream infections, previous infections, or with colonization alone.

Clinical Manifestations

Invasive *Candida* Infections

Skin-Invasive Infections

Congenital Cutaneous Candidiasis

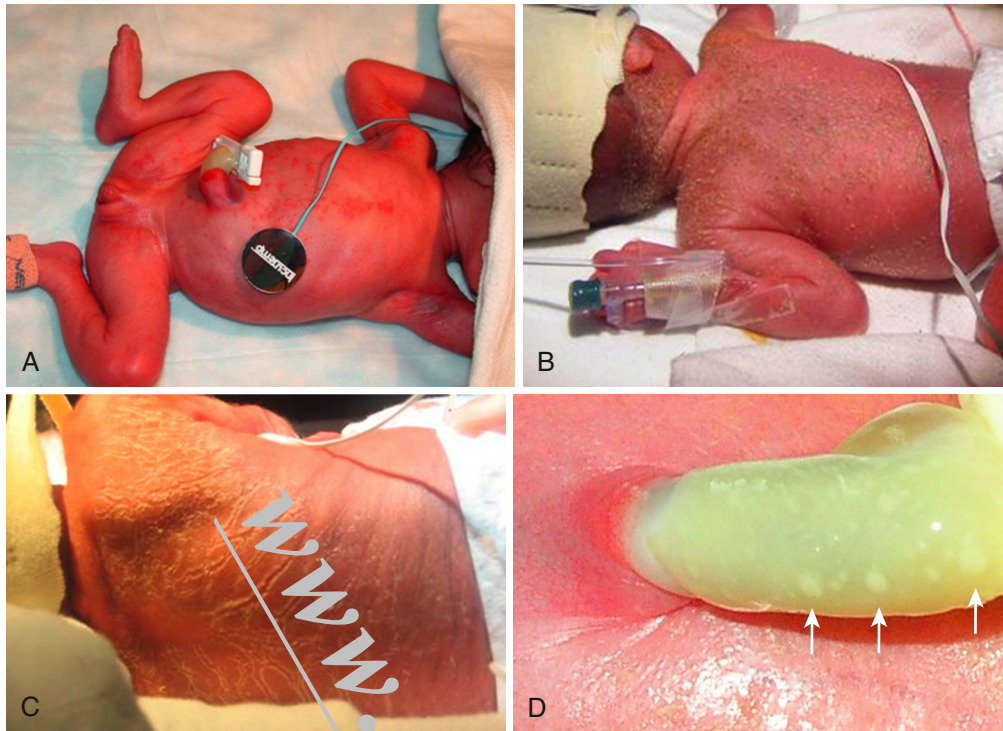
CCC (Table 51.3, Fig. 51.7) presents most commonly at birth but can occur within the first week. Dermatologic

TABLE 51.3

Cutaneous Candidiasis Definition

Presentation	Extensive <i>Candida</i> Skin Rash <ul style="list-style-type: none"> • Covering 2 or more affected areas (see below) OR • Covering 1 affected area (see below) PLUS umbilical plaques or placental pathology (silver or H&E) would count as 1 affected area
Affected Areas	Skin <ul style="list-style-type: none"> • Chest • Abdomen • Back • Extremity • Groin or perineal area • Neck • Face or scalp Umbilical Cord and Placenta <ul style="list-style-type: none"> • White plaques on umbilical cord • Placenta with yeast invasion
Skin Rash	<ul style="list-style-type: none"> • Erythematous maculopapular • Papulopustular • Scaly • Dry, flaking • Desquamating • Burnlike erythematous
Timing	Congenital Cutaneous Candidiasis <ul style="list-style-type: none"> • Presenting in the 1 week after birth—most commonly present at birth to 3 days Cutaneous Candidiasis <ul style="list-style-type: none"> • Presenting after 7 days of life
Evaluation	Congenital Cutaneous Candidiasis <ul style="list-style-type: none"> • Culture skin rash (≥ 2 sites) (aerobic culture) • Blood, CSF (unless rash over back), and urine (if >72 h) cultures • Send umbilical cord and/or placenta for pathology/silver stain Cutaneous Candidiasis <ul style="list-style-type: none"> • Skin rash sites, blood, urine, CSF (unless rash over back)
Diagnosis	Skin Findings and 1 or More of the Following: <ul style="list-style-type: none"> • Surface culture isolating <i>Candida</i> species • Placental or cord identification (culture or silver stain) of yeast or <i>Candida</i> species for congenital cutaneous candidiasis • Positive blood, urine, CSF cultures for <i>Candida</i> species
Treatment	<ul style="list-style-type: none"> • 14-day course of systemic antifungal therapy

CSF, Cerebrospinal fluid.



• **Fig. 51.7** Congenital cutaneous candidiasis. (A) Macular papular rash. (B) Dry, flaky rash. (C) Dry, crackling scaly rash. (D) White plaques of the umbilical cord. (From Kaufman DA, Coggins SA, Zanelli SA, et al. Congenital cutaneous candidiasis: prompt systemic treatment is associated with improved outcomes in neonates. *Clin Infect Dis*. 2017;64:1387–1395.)

findings include desquamating maculopapular, papulopustular, and/or erythematous rashes. The most common finding from a recent study included desquamation alone (scaling, peeling, flaking, or exfoliation) or with other rash presentations.²⁹ CCC usually occurs only as a rash but dissemination such as pneumonia or BSI may also be present. Without prompt identification and systemic treatment, dissemination to the blood, urine, or cerebrospinal fluid (CSF) can occur in infants with CCC ranging from 11% in term infants to 33% in infants 1000 to 2500 g and highest at 66% in infants less than 1000 g.³⁰ A study examining the pathology and pathogenesis of CCC demonstrated a high burden of yeast with invasion into the epidermis and dermis with inflammation and injury including granulomas, focal necrosis, and hemorrhage. These data from biopsies give insight into the invasive nature of the cutaneous involvement. For these reasons, preterm and term infants should be treated promptly at the time of rash presentation with systemic antifungal therapy and for a minimum of 14 days similarly to other invasive fungal infections. Delaying systemic treatment, solitary use of topical therapy (nystatin), and treating for less than 10 days are associated with *Candida* dissemination to the bloodstream.²⁹

By culturing for both fungal and bacterial organisms by performing aerobic skin cultures of the rash, the source of infection can be confirmed in a timely fashion, but empiric therapy should be administered at time of rash presentation. Differential diagnosis includes staphylococcal as well as other bacterial and fungal skin infections. Pathology with

angular staining of the umbilical cord and placenta can also aid in diagnosis.

Cutaneous Candidiasis

Cutaneous candidiasis, referred to in past literature as mucocutaneous infection, presents with similar skin manifestations to CCC but occurs later than CCC. In the era before antifungal prophylaxis, the incidence was reported to be as high as 8% in VLEW infants. Risk factors include extreme prematurity, vaginal birth, postnatal steroids, and hyperglycemia. The importance of candida-like dermatitis often goes unrecognized before dissemination to the blood. Cutaneous candidiasis, similar to CCC, is an invasive infection of the skin; empiric therapy should be started at the time of rash presentation and needs treatment for a minimum of 14 days in preterm infants.

Bloodstream Infection

Candidemia

Clinical signs and symptoms of candidemia are similar to bacteremia (Table 51.4). Most importantly, candidemia can be associated with disseminated disease (see End-Organ Dissemination). Evaluation of cardiac, liver, renal, ophthalmologic, and central nervous systems is warranted and discussed in the following.

Renal Candidiasis

Candida infection of the kidney may occur because of an ascending UTI or via hematogenous spread. Studies demonstrate that

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