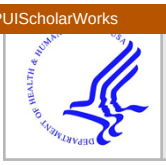

Published in final edited form as:
Cardiol Young. 2016 January ; 26(1): 30–52. doi:10.1017/S1047951115001389.

CHD associated with syndromic diagnoses: peri-operative risk factors and early outcomes

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Abstract

CHD is frequently associated with a genetic syndrome. These syndromes often present specific cardiovascular and non-cardiovascular co-morbidities that confer significant peri-operative risks affecting multiple organ systems. Although surgical outcomes have improved over time, these co-morbidities continue to contribute substantially to poor peri-operative mortality and morbidity outcomes. Peri-operative morbidity may have long-standing ramifications on neurodevelopment and overall health. Recognising the cardiovascular and non-cardiovascular risks associated with specific syndromic diagnoses will facilitate expectant management, early detection of clinical problems, and improved outcomes – for example, the development of syndrome-based protocols for peri-operative evaluation and prophylactic actions may improve outcomes for the more frequently encountered syndromes such as 22q11 deletion syndrome.

Keywords

CHD; syndrome; genetic

CHD is present in 3–12 in 1000 births, but the incidence may be as high as 5% when strictly including all cardiovascular malformations such as bicuspid aortic valve.[1–5] The genetic basis of CHD is well established[4] – for instance, the Baltimore–Washington Infant Study in 1989 reported chromosomal abnormalities in nearly 13% of infants with CHD.[6] More recent studies have observed that 20–30% of infants with CHD have a recognised genetic syndrome or significant non-cardiovascular anomaly.[5,7,8] Even among patients with isolated CHD, there is evidence for heritability and increased familial recurrence risk that may be particularly important for certain classes of CHD such as heterotaxy, left ventricular outflow tract obstructive lesions, and atrioventricular septal defects.[9,10] In a minority of cases, gene mutations in *NKX2–5, GATA4*, and *NOTCH1* have been observed in families demonstrating Mendelian inheritance.[11–13] With the advancement of genetic technologies including DNA microarray and high-throughput sequencing platforms detection of genetic causes of CHD

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Conflicts of Interest
None.

Supplementary materials
For supplementary materials referred to in this article, please visit http://dx.doi.org/10.1017/S1047951115001389

continues to grow rapidly.[14–16] It is critical that clinicians recognise the clinical relevance of a genetic diagnosis in order to improve outcomes, not only for syndromic patients but also for all CHD patients with informative genotypes. The peri-operative time period exposes patients to risk for significant complications that may have both immediate and long-term repercussions, including quality of life or neurocognitive outcomes.[17,18] The aims of this review were to present the spectrum of peri-operative risks for patients with a genetic syndrome and CHD, comprehensively organise observations about the outcomes of patients with genetic syndromes, and synthesise our current understanding of the genetic basis of CHD as a tool for informing the peri-operative management of these patients.

Advances in cardiac surgery, catheterisation, and intensive care have significantly reduced mortality associated with CHD,[19] shifting the focus towards minimising short- and long-term morbidity. There are well-recognised peri-operative risks for all children undergoing cardiac surgery, including but not limited to myocardial dysfunction, arrhythmias, respiratory failure, infection, bleeding, thrombosis, kidney injury, and neurological injury.[20] However, the CHD sub-population with syndromic disease often has important non-cardiovascular and functional – that is, non-structural – cardiovascular abnormalities that significantly modify these routine peri-operative risks or present additional risks that contribute to morbidity and mortality. It is certain that the cardiac surgeon, anaesthesiologist, intensivist, and cardiologist will frequently encounter children with a syndromic disorder. To our knowledge, the specific peri-operative risks that exist for patients with CHD and genetic syndromes have not previously been consolidated into a single source.

Many large studies have enrolled syndromic patients to broadly evaluate the impact of a syndromic diagnosis on surgical outcomes

Widely inclusive studies, which have analysed all types of paediatric cardiac surgical operations together, have observed that a syndromic diagnosis may not impact early operative mortality but does predispose to post-operative complications contributing to prolonged hospital length of stay.[21–24] However, batching all types of CHD in this manner provides limited insight into risk factors, as both the genetic basis and the risk profiles of different cardiac lesions vary. Sub-classes of cardiac lesions that have been studied specifically include critical left ventricular outflow tract obstructive lesions and conotruncal defects. Detailed information about these studies, including study types, enrollment numbers, cardiac and genetic diagnoses, and early mortality and morbidity outcomes, is provided in Supplementary Table S1.

Patel et al[25] extensively reviewed early post-operative outcomes data for hypoplastic left heart syndrome/critical left ventricular outflow tract obstruction from both the Society of Thoracic Surgeons – ~1200 Norwood operations from 2002 to 2006 – and the Congenital Heart Surgeons' Society ~700 stage 1 palliations from 1994 to 2001 – databases. In the Society of Thoracic Surgeons database, 15% of patients were documented to have a "genetic and/or significant non-cardiovascular abnormality", which was associated with increased in-hospital mortality (26.7 versus 19.8%). Similarly, in the Congenital Heart Surgeons' Society database, 8% had a "non-cardiac congenital abnormality or syndrome", which was

associated with increased early risk of mortality. These mortality data are consistent with two other single-centre reports (together 310 patients)[26,27] and with data from the Pediatric Heart Network's Single Ventricle Reconstruction trial including 549 patients undergoing Norwood operations.[28] This evidence is countered only by a single series of 158 patients who underwent Norwood operation.[29] The Society of Thoracic Surgeons data demonstrate that in-hospital mortality was not increased after stage 2 (~700 operations) or stage 3 palliations (~550 operations), recognising that stage 1 mortality may limit interpretation.[25] Increased morbidity was observed after all stages of palliation.[25,30]

Michielon et al[31] provided important perspective in a cohort of nearly 800 patients with conotruncal defects – tetralogy of Fallot with or without pulmonary atresia, double-outlet right ventricle, truncus arteriosus, or interrupted aortic arch – undergoing biventricular repair from 1992 to 2007. Uniquely, nearly every patient in the cohort (96%) underwent clinical evaluation by a geneticist and prospective molecular screening (93%) for 22q11 deletion or aneuploidy. A genetic diagnosis was established in ~27% of these patients and was associated with increased hospital mortality (17 versus 7%) and prolonged duration of intensive care. These findings were consistent with previous observations in 266 patients with tetralogy of Fallot with normal pulmonary artery anatomy.[32] Similarly, a cohort of 350 patients with conotruncal defects undergoing primary or staged repair trended towards increased early mortality.[33]

Taken together, the presence of a genetic syndrome may negatively impact early post-operative survival, particularly in the context of more complex cardiac operations such as the Norwood operation. It is particularly clear that post-operative morbidity risk is consistently elevated across the spectrum of cardiac lesions. These are very important observations, but are based on data from heterogeneous groups of genetic syndromes, which limit generalisability to specific syndromes. Moreover, batching patients with non-cardiovascular malformations lacking a defined genetic syndrome together with those who have a defined genetic syndrome creates challenges. In order to understand the risk factors and clinically intervene to improve outcomes, more precise data are required. To this end, the remainder of this article focuses on outcomes and risk factors for specific syndromic CHD populations.

The presence of a specific genetic syndrome impacts early peri-operative outcomes, and genetic syndromes often present with specific features posing significant peri-operative risks

Down syndrome

Down syndrome is present in at least one in 1000 live births and is caused by trisomy of chromosome 21 due to true aneuploidy, unbalanced translocation, or mosaicism.[34,35] Approximately 40–50% of patients with Down syndrome present with CHD, most frequently atrioventricular septal defect, followed by ventricular septal defect, atrial septal defect, patent ductus arteriosus, and tetralogy of Fallot.[34,36]

Survival after cardiac surgery is generally favourable, as summarised in Table 1, with more detailed information in Supplementary Table S2; three large contemporary database reviews

– encompassing a spectrum of cardiac operations and cumulatively including nearly 7000 patients with Down syndrome – demonstrated that in-hospital mortality risk decreased (Healthcare Cost and Utilization Project Kids' Inpatient Database)[37,38] or was not different (Society of Thoracic Surgeons database)[39] when compared with children without Down syndrome. Cardiac lesions studied specifically in Down syndrome are atrioventricular septal defects, conotruncal defects (primarily tetralogy of Fallot), and single ventricle lesions. Poor outcomes after repair of atrioventricular septal defects were reported in early surgical eras,[40,41] but recent evidence indicates that children with Down syndrome undergoing biventricular repair for complete atrioventricular septal defect have better[37,42] or similar early mortality rates[43–46] compared with patients without Down syndrome. Re-operation rates may be lower in Down syndrome, likely related to less complex atrioventricular valve and outflow tract anatomy.[42–44,46] Increased risk for post-operative complete heart block is reported after ventricular septal defect repair[39,47] but not after atrioventricular septal defect repair.[42,48]

Similar to complete atrioventricular septal defect repair, Down syndrome does not significantly impact early mortality after surgery for tetralogy of Fallot[32,37,39,41,49] or conotruncal defects collectively (predominantly tetralogy of Fallot).[31,33] In contrast, Down syndrome may significantly worsen outcomes for single ventricle lesions. Review of the Kids' Inpatient Database found that early mortality was increased both after systemic-to-pulmonary shunt placement and after stage 2 palliation.[37] Review of the Society of Thoracic Surgeons database also demonstrated increased hospital mortality for all stages of single ventricle palliation.[39] Increased mortality (35%) after stage 3 palliation was observed in the Pediatric Cardiac Care Consortium database[50] but was not corroborated by the Kids' Inpatient Database or a smaller single-centre series.[37,51] The reasons for poor outcomes after single ventricle palliations in these patients are undefined but likely related to predisposition for pulmonary hypertension, which may also contribute to prolonged hospitalisation after stage 2 and stage 3 palliations.[39,51]

Many features of Down syndrome impact peri-operative morbidity. Pulmonary and pulmonary vascular co-morbidities feature prominently (Table 2 and Supplementary Table S3). Congenital respiratory tract anomalies may be present at multiple levels and include macroglossia/glossoptosis, adenotonsillar hypertrophy, sub-glottic stenosis, laryngomalacia, tracheal stenosis, complete tracheal rings, and tracheobronchomalacia. Hypotonia can exacerbate anatomical narrowing. Patients are at risk for pulmonary hypertension due to chronic hypoventilation related to airway obstruction and sleep apnoea as well as intrinsic risk for pulmonary vascular disease.[52–54] Craniofacial and upper airway anomalies can complicate peri-operative airway management and/or performance of trans-oesophageal echocardiography.[55–57] Pulmonary abnormalities include pulmonary hypoplasia, interstitial lung disease secondary to chronic aspiration or infection, tracheal bronchus predisposing to recurrent right upper lobe collapse or pneumonia, sub-pleural cysts predisposing to pneumothorax, and lymphatic abnormalities including pulmonary lymphangiectasia.[58–63] These airway co-morbidities manifest clinically as increased risk for post-operative respiratory complications,[39,48,64] prolonged mechanical ventilation,[51,64,65] pneumothorax,[48] chylothorax,[22,39] chylopericardium,[66] and failed extubation.[67] These observations mandate vigilant assessment and treatment of the pulmonary status in the post-operative period,

which may be optimised by pre-operative consultation and testing, particularly in high-risk patients – for example, single ventricle lesions.

Dysfunction of B- and T-lymphocytes and neutrophils may predispose to infections and exacerbate the inflammatory response to cardiopulmonary bypass.[22,39,48,51,68–71] Congenital hypothyroidism occurs in ~1%, and thyroid screening at regular intervals, including at ages 6 and 12 months, is indicated because an additional 4–18% develop hypothyroidism.[34,72,73] Pre-operative thyroid screening is indicated so that hypothyroidism can be treated pre-operatively. As thyroid levels decrease with cardiopulmonary bypass surgery and impact myocardial function and cardiovascular stability,[74,75] intra-operative and post-operative parenteral therapy may be indicated. The risk for atlantoaxial instability calls for appropriate peri-operative precautionary measures to avoid neurological injury, especially in mid-to-late childhood.[34,76] Increased risk for seizures – ~ 8% in the general Down syndrome population – should also be considered.[77] Taken together, Down syndrome presents significant co-morbidities that can impact peri-operative outcomes. Fortunately, mortality outcomes have improved over time for the most-frequent lesions, but non-cardiovascular abnormalities continue to contribute to post-operative morbidity outcomes and require clinical vigilance and future research.

22q11 deletion syndrome

Microdeletion of 22q11.2 causes several disorders with overlapping clinical phenotypes including DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome, and is present in approximately one in 5000 live births.[78,79] Suggestive features include long narrow face and small protuberant ears with thick and crumpled helices.[80] CHD is present in at least 75%.[81] The typical cardiac lesions are conotruncal defects and abnormalities of the aortic arch and brachiocephalic arteries, including type B interrupted aortic arch, truncus arteriosus, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, isolated ventricular septal defect, and abnormal aortic arch sidedness and/or branching.[82–84]

Peri-operative outcomes are summarised in Table 1 with more detailed information in Supplementary Table S4. Early reports observed very high operative mortality in neonates with DiGeorge syndrome.[85] Although increased hospital mortality was also observed in a more contemporary series of patients with conotruncal defects,[33] there is strong evidence that 22q11 deletion no longer results in early mortality for the vast majority of cardiac lesions;[31,32,86–88] however, substantial post-operative morbidity persists including slow recovery and increased frequency of cardiac events such as the need for re-operation.[31,32,86,87] Notably, patients with pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries have consistently demonstrated increased early mortality in the setting of 22q11 deletion.[89–93] In addition, early operative mortality after Norwood stage 1 operation was observed in two of five patients in the Congenital Heart Surgeons' Society database from 1994 to 2001, supporting the concept that genetic syndromes continue to impact high-risk operations.[25]

Congenital malformations including cleft palate, sub-mucous clefts, retrognathia, Pierre Robin sequence, congenital laryngeal web, and vascular ring may complicate airway

management.[81,94,95] Bronchomalacia and bronchospasm have been observed in patients with 22q11 deletion and pulmonary atresia with ventricular septal defect, which may be related to compression by aortopulmonary collateral vessels.[96,97] Although prolonged mechanical ventilation was not observed after unifocalisation of the major aortopulmonary collateral arteries,[98] increased post-operative respiratory complications including prolonged intubation and post-extubation stridor have been observed.[99]

Thymic aplasia occurs rarely (<1% of cases) and is associated with severe immune deficiency. More commonly, thymic hypoplasia causes mild-to-moderate immune deficiency. Complete preoperative immunological evaluation and blood product precautions – cytomegalovirus-negative and irradiated blood products – are indicated for all cases to prevent iatrogenic infection and graft versus host disease.[80,85,100] Low T-lymphocyte counts are present in 75–80% of patients with 22q11 deletion.[101] B-lymphocyte dysfunction with immunoglobulin deficiency also may have clinical significance.[102,103] Frequent infectious complications including fungal infections have been reported[23,85,88,91,99] but not uniformly.[86,87,90] It has been suggested that prophylaxis with broad-spectrum antibiotics including antifungal agents may be indicated.[104] Developmental hypoplasia of the parathyroid glands results in hypocalcaemia in 40–80% of patients and is often accompanied by hypomagnesaemia.[105] Close peri-operative electrolyte monitoring is necessary to preserve cardiac function, avoid dysrhythmia, and prevent secondary seizures. Peri-operative seizures are linked to worse neurodevelopmental outcomes in 22q11 deletion.[106] Annual assessment of thyroid function is recommended because hypothyroidism is present in 20–30% of patients; a routine preoperative thyroid screening approach similar to Down syndrome may be reasonable.[80,105,107]

Interestingly, the gene encoding glycoprotein Ib (*GP1BB*), which is responsible for autosomal-recessive Bernard–Soulier disease, is located within the 22q11 region. Patients with 22q11 deletion, and thus hemizygous deletion of *GP1BB*, may have abnormally large platelets and thrombocytopaenia (macrothrombocytopaenia).[108,109] Platelet dysfunction has been described previously.[110,111] Post-operative bleeding accounted for a significant proportion of post-operative deaths in patients with pulmonary atresia with ventricular septal defect.[90,93] A complete haematological workup may be indicated before operations requiring small vessel anastomoses – for example, unifocalisation – and unexplained severe post-operative bleeding should trigger concern for Bernard–Soulier disease due to mutation of the nondeleted *GP1BB* allele.[112] Renal and urinary tract abnormalities are present in 30–40% of patients, including renal agenesis, multi-cystic dysplastic kidneys, hydronephrosis, and vesicoureteral reflux.[81,113] Increased need for post-operative dialysis has been observed.[88] Autonomic dysfunction may in some cases explain post-operative hypotension refractory to usual therapy.[114] Taken together, the developmental abnormalities associated with 22q11 deletion likely contribute to mortality after complex operations and morbidity across the spectrum of CHD surgery. Improvements in anticipatory management of common abnormalities – for example, immune dysfunction and hypocalcaemia – will continue to improve outcomes. Abnormalities that are less frequently recognised – for example,. haematological dysfunction – should be anticipated and acted upon when deviation from expected recovery is encountered.

Heterotaxy syndrome

Heterotaxy syndrome, a disorder of laterality characterised by abnormal thoracoabdominal situs, is frequently associated with CHD and is present in at least one in 10,000 live births.[115] Mutations in genes such as *DNAH5, ZIC3, CFC1, NODAL, ACVR2B, DNAI1*, and *LEFTY2*, many of which are components of the Nodal signal transduction pathway, have been identified;[116] familial recurrence is more frequently observed compared with other cardiac lesions.[9] CHD is often complex, including complete atrioventricular canal defect, anomalous pulmonary and systemic venous return, and pulmonary outflow tract obstruction. Heterotaxy can be sub-classified as right atrial isomerism versus left atrial isomerism as determined by atrial appendage and bronchopulmonary anatomy.[117] In general terms, right atrial isomerism typically has more severe CHD, often requires single ventricle palliation, and has worse survival in childhood.[118–120] In right atrial isomerism, abnormal morphology and function of the sinoatrial node and the atrioventricular conduction system predispose to both tachyarrhythmia and bradyarrhythmia[121–124] – for instance, supra-ventricular tachycardia has been observed in up to 25% of cases, including re-entrant mechanisms mediated by twin atrioventricular nodes.[125–127] Atrioventricular block and sinus node dysfunction are more frequently observed in left atrial isomerism.[125,127] In addition to arrhythmia concerns, non-compaction cardiomyopathy is described and may contribute to unexpected ventricular dysfunction.[128]

Peri-operative outcomes in heterotaxy are summarised in Table 1 and Supplementary Table S5. The complexities of both cardiovascular and noncardiovascular abnormalities likely contribute to poor outcomes.[120] Increased mortality following any cardiac surgery has been observed in the Society of Thoracic Surgeons' database.[129,130] Mortality after initial single ventricle palliation is reported to range from 10 to 23%.[121,129,131,132] In the setting of total anomalous pulmonary venous return, poor outcomes may be related to hypoplastic pulmonary veins and increased pulmonary vascular reactivity.[131–133] Despite these challenges, there was similar survival between heterotaxy and non-heterotaxy patients undergoing primary repair for total anomalous pulmonary venous return but increased need for pulmonary vein re-operation.[134] Mortality rates after stage 3 palliation ranged widely from as high as 19–43%[123,135,136] to as low as 3–4% in recent studies.[123,124,129] Complex anatomy can potentially complicate cardiac transplantation but did not impact early (or late) graft survival;[137] however, early mortality was recently reported in two of five patients undergoing cardiac transplantation.[138] Overall, there is strong evidence that heterotaxy confers significant peri-operative mortality risk.

Post-operative respiratory morbidity was frequently observed.[130] Up to 40% of patients with heterotaxy and CHD have dysfunctional airway cilia similar to primary ciliary dyskinaesia.[139] Indeed, ciliopathy is a suspected developmental mechanism for cardiovascular and non-cardiovascular malformations.[116] Respiratory ciliary dysfunction, diagnosed by nasal nitric oxide levels or nasal video microscopy, has been associated with post-operative respiratory complications, including failed extubation, respiratory failure, respiratory infection, stridor, pleural effusion, atelectasis, pneumothorax, or pulmonary oedema, as well as with the need for tracheostomy.[140] It has been suggested that beta-agonist therapy may be effective by improving ciliary motility.[140,141]

Splenic abnormalities including asplenia (often left atrial isomerism) polysplenia (often right atrial isomerism) or the presence of accessory splenule are frequently observed.[142] Asplenia clearly increases risk of bacterial infections in children.[143] Splenic function in the setting of polysplenia may also be impaired and should be evaluated using scintigraphy.[144] Sepsis was the cause of early post-operative mortality in 13% of deaths in a large heterotaxy population.[145] Oropharyngeal malformations including micrognathia, choanal atresia, and cleft lip/palate can contribute to airway management difficulties.[146,147] Renal anomalies including renal agenesis, cystic malformation, and horseshoe kidney are also frequently observed.[132,147]

The surgical outcomes in heterotaxy are improving, but persistent challenges include complex anatomy such as abnormal cardiac position, hypoplastic and anomalous pulmonary veins, and single ventricle morphology, predisposition for arrhythmia, and pulmonary and immunological dysfunction.

Turner syndrome

Turner syndrome occurs in approximately one in 2000 female live births and is caused by complete or partial absence of the X chromosome.[148,149] Features include short stature, ovarian dysgenesis, webbed neck, low posterior hairline, and widely spaced nipples.[150] There is a high rate of foetal mortality, often in the setting of foetal hydrops.[151] Those surviving to birth often have cardiovascular malformations including bicuspid aortic valve, coarctation of the aorta, partial anomalous pulmonary venous return, persistent left superior caval vein, and hypoplastic left heart syndrome.[152–155] Turner syndrome accounts for at least 5% of coarctation of the aorta among girls, which may indicate karyotype screening of all female neonates with coarctation.[156] There is also significant long-term risk of aortic dilation and dissection that is likely under-recognised.[157,158] Electrocardiographic abnormalities including prolonged QT interval are frequently encountered, but risk of life-threatening arrhythmia has not been established.[159]

Turner syndrome does not appear to increase mortality risk after repair of coarctation of the aorta but has been associated with longer hospitalisation (Table 1 and Supplementary Table S6).[160] By comparison, mortality appears to be significantly increased in patients with hypoplastic left heart syndrome – for instance, 9 out of 11 infants with Turner syndrome undergoing Norwood stage 1 operation died by 4 months of age as per the Congenital Heart Surgeons' Society database.[25] In a retrospective single institution study, 8 out of 10 infants with Turner syndrome undergoing stage 1 palliation for hypoplastic left heart syndrome died before stage 2 operation, and both the survivors were mosaic XO.[161] In a more recent series, all four patients with Turner syndrome undergoing stage 1 palliation survived to hospital discharge, but three were reported to have died before stage 3 palliation.[160] A precise explanation for these outcomes has not been established thus far, but lymphatic abnormalities may contribute.[161] Automatic karyotype screening in girls with hypoplastic left heart syndrome may be indicated because some features develop over time or may be subtle in mosaic cases.

Predisposition to vascular complications were described in earlier case series that reported significant post-operative haemorrhage and risk for aortic rupture, possibly related to

increased arterial tissue fragility and peri-operative systemic hypertension.[162,163] Fortunately, improvements in surgical technique and intensive care have effectively reduced post-operative bleeding risk. Morphological abnormalities such as elongation of the transverse arch (present in 50% of cases) may impact surgical approach,[152] which may lead to longer cross-clamp time during coarctation repair.[160] Although unlikely to develop in the early post-operative period, there is established risk for dissection after surgical repair or transcatheter stenting of aortic coarctation.[164–166] Small case series have provided evidence that balloon angioplasty or stent placement for coarctation is safe and effective in the short term,[167,168] but covered stents may be the best approach in the context of intrinsically abnormal arterial tissue.

The non-cardiovascular abnormalities that potentially impact peri-operative risk and outcomes include the lymphatic, renal, and endocrine systems. Lymphatic dysfunction can present as foetal lymphoedema or pulmonary lymphatic anomalies such as congenital pulmonary lymphangiectasia, which may predispose to post-operative chylothorax.[169] Postnatal peripheral lymphoedema may be a clue to Turner syndrome diagnosis but has no clear clinical impact and usually resolves by 2 years of age without intervention.[149] Abnormalities of the renal and urinary system are present in 30–40% of patients, including horseshoe kidney in 10%.[149] Hypothyroidism develops in up to 25% of cases, most commonly autoimmune related, and annual thyroid screening is recommended starting at 4 years of age.[149,170] In summary, Turner syndrome most clearly impacts outcomes for hypoplastic left heart syndrome. Further investigation is needed to explain these poor outcomes and develop novel approaches and interventions. Arteriopathy associated with Turner syndrome predisposes to hypertension and aortic complications, such as dissection, mandating acute peri-operative blood pressure management and longitudinal follow-up.

Williams syndrome

Williams syndrome occurs in approximately one in 10,000 live births[171] and is associated with 7q11.23 microdeletion. Haploinsufficiency of the elastin gene (*ELN*) is responsible for the cardiovascular manifestations. Facial features during infancy include a short upturned nose with a flat nasal bridge, peri-orbital puffiness, and long philtrum and later develop into full lips, wide smile, and coarse appearance. Relative strengths in verbal skills and social personality may belie intellectual disability that is present in most cases.[172] Familial supra-valvar aortic stenosis is associated with *ELN* mutations and presents with similar cardiovascular features but none of the non-cardiovascular features.

The spectrum of vascular manifestations in Williams syndrome is consistent with generalised arteriopathy. The majority of patients with Williams syndrome have supra-valvar aortic stenosis (45–75%), which may be “hourglass” or “diffuse” type.[173] Severe supra-valvar aortic stenosis is unlikely to regress and can be progressive,[174–176] but mild stenosis is likely to remain stable.[176–178] Additional vascular findings include branch pulmonary stenosis, peripheral pulmonary artery stenosis, supra-valvar pulmonary stenosis, and stenosis of the thoracic aorta, as well as bicuspid aortic valve and mitral valve prolapse.[173] The pulmonary arterial lesions often spontaneously improve or resolve over time,[174–176,178] but regression also is less likely when severe stenosis is present.[179] Surgical repair of supra-

valvar aortic stenosis in patients with Williams syndrome has good mortality outcomes with no significant difference in long-term survival compared with familial or sporadic supra-valvar aortic stenosis.[180] On the other hand, early mortality can be as high as 20% for cases presenting with the combination of severe supra-valvar aortic stenosis and moderate-to-severe pulmonary stenosis.[179,181]

Balloon angioplasty of supra-valvar aortic stenosis has been dispelled due to lack of success.[176] After transcutaneous stent placement for native or residual post-operative aortic coarctation, there is significant risk for developing re-stenosis, characterised by fibrosis and vascular smooth muscle cell proliferation.[182,183] Indeed, patients with stenosis of the thoracic aorta have high re-intervention rates.[184] The pulmonary arteries are also predisposed to re-stenosis, aneurysm formation, intimal flap formation, dissection, and rupture after catheter-based interventions.[185,186] These outcomes indicate that arteriopathy may limit the effectiveness and increase risk factors when performing catheter-based interventions for arterial stenoses.

It is critical to recognise the risk of sudden cardiac death in patients with Williams syndrome, particularly during procedural sedation or anaesthesia or coronary angiography.[179,187–190] This risk is highest in those with coronary ostial stenosis or severe biventricular outflow tract obstruction. Among 242 patients with Williams syndrome undergoing 435 cardiac operations or catheter-based interventions, described in the Pediatric Cardiac Care Consortium database, 12 of 15 deaths occurred in the setting of biventricular outflow tract obstruction.[185] Coronary ostial stenosis is present in at least 5% of cases and is more common in the “diffuse” type of supra-valvar aortic stenosis or when stenosis of the thoracic aorta is present.[178,191] Potential mechanisms of coronary stenosis include adhesion of aortic valve leaflets, overhanging of the supra-valvar ring, or reactive changes to hypertension. Coronary artery stenosis can develop during childhood in the absence of supra-valvar aortic stenosis,[192,193] and dilation and tortuosity of the coronary arteries are well recognised.[194] These observations suggest primary arteriopathic mechanisms. QT interval prolongation is present in up to 15% of cases, which may predispose to ventricular dysrhythmia and also contribute to sudden death risk.[195,196] As coronary stenosis can be sub-clinical, it is critical that patients undergo complete assessment of the coronary arteries when appropriate and that providers be cognizant of the risk factors for sudden death around the time of interventional procedures.

Systemic hypertension develops in up to 50% of individuals, which is secondary to renal artery stenosis in some cases. In most cases, hypertension may rather be due to abnormal vascular function or morphology in the distal arteries, but the precise mechanisms are not well understood.[197] Cerebral artery stenosis causing ischaemic stroke has been observed in children and should be suspected if neurological changes develop.[198] Selecting target blood pressure ranges around the time of procedures can be complicated by the presence of pre-existing hypertension combined with coronary or cerebral artery stenosis, which requires highly attentive pre-operative and post-operative care.

Owing to a 15–30% prevalence of sub-clinical hypothyroidism, often due to thyroid hypoplasia, thyroid function testing is recommended every 4 years, and pre-operative

evaluation should include thyroid function tests and clinical evaluation for symptoms.[199–202] Congenital hypothyroidism due to severe thyroid hypoplasia has also been reported.[203] Airway management may be challenging due to facial dysmorphism.[200] Based on a concern for mild myopathy in some patients, there have been recommendations to avoid the use of succinylcholine and closely monitor the effects of non-depolarising neuromuscular blockade.[200] Anomalies of the kidneys and urinary tract, such as renal aplasia, kidney duplication, horseshoe kidney, and bladder diverticuli, are present in up to 40% of the cases.[204,205] Proteinuria was observed in 25%of patients, suggesting that kidney function should be monitored closely.[206] Although there is predisposition for episodic hypercalcaemia and hypercalciuria, particularly as neonates, nephrocalcinosis is uncommon.[207]

Taken together, severe vascular stenosis of the systemic and/or pulmonary arteries increase risk, and asymptomatic patients may be at risk for sudden cardiac death in the setting of occult coronary artery stenosis. These risks pertain to cardiac and non-cardiac procedures.

Noonan syndrome and related disorders

Noonan syndrome has a prevalence of one in 1000–2500 live births.[208] Disease-causing mutations in genes associated with the RAS-MAPK signaling pathway, such as *PTPN11* (most frequent), *SOS1, RAF1, KRAS, NRAS, BRAF, SHOC2*, and *CBL*, are identified in up to 60% of the cases.[209] Cardiofaciocutaneous syndrome (*BRAF, KRAS*) and Costello syndrome (*HRAS*) are disorders related to Noonan syndrome with overlapping phenotypic features and genetic aetiologies.[210] Neonatal features of Noonan syndrome include tall forehead, hypertelorism, arched eyebrows, low-set posteriorly rotated ears with thick helices, low posterior hairline, and excessive nuchal skin.[209] Many of these features become more subtle over time, but short stature, pectus deformity, and neck webbing often remain prominent.[208] Patients with Noonan syndrome often achieve normal intelligence,[211] whereas cardiofaciocutaneous and Costello syndromes often have more significant developmental delay.[210,212]

At least 80% of patients with Noonan syndrome have cardiac lesions including pulmonary valve stenosis (50–60%) and secundum atrial septal defect (6–30%).[208,213] Hypertrophic cardiomyopathy is present in ~ 20% of patients, especially *RAF1* mutations, and portends worse survival than nonsyndromic hypertrophic cardiomyopathy;[214,215] however, spontaneous regression occurred in nearly 20% of patients diagnosed in infancy.[213] Fibromuscular dysplasia with clinically significant narrowing of the coronary arteries has been reported in the setting of Noonan syndrome and hypertrophic cardiomyopathy.[216] Electrocardiographic abnormalities are frequently observed, including predominantly negative forces in the left pre-cordial leads, left axis deviation, and abnormal Q waves.[217] Although there are no particular rhythm abnormalities associated with Noonan syndrome, individuals with Costello syndrome (*HRAS* mutation) develop atrial tachycardia (often multi-focal) in ~50% of cases.[218] Early post-operative mortality outcomes have not been frequently reported in Noonan syndrome. Cardiac transplantation in the setting of Noonan syndrome is described, but outcome data are similarly scant.[219] Longitudinal screening for occult hypertrophic cardiomyopathy may be indicated, particularly among those with

PTPN11 or *RAF1* mutations, in part to mitigate risk during cardiac and non-cardiac procedures.

Systemic features most likely to impact perioperative outcomes are haematological and lymphatic abnormalities. Haematological abnormalities such as platelet dysfunction and coagulation factor deficiency are present in 30–65% of cases.[209,220–223] Severe congenital thrombocytopaenia has been described.[224] A recent study reported frequent easy bruising and post-surgical bleeding (15–25%), platelet dysfunction (80%), and factor VII deficiency (20%).[225] Bleeding diathesis may predispose patients to spontaneous gastrointestinal or sub-arachnoid haemorrhage, which may respond to administration of recombinant factor VII.[226,227] Owing to the risk of coagulopathy, complete blood count and basic coagulation testing is warranted before operations, haematology consultation should be considered, and aspirin may be avoided.[208,209]

Lymphatic abnormalities are observed in ~20% of cases.[209] Peripheral lymphoedema often spontaneously resolves within the first several years but can have late onset.[228] Similar to Turner syndrome, pulmonary lymphatic abnormalities including congenital pulmonary lymphangiectasia may predispose to chylothorax.[169,229–231] Post-operative pericardial and pleural effusions were not significantly increased in a series of ~120 operations.[213] Cutaneous leaking of lymphatic fluid from a femoral vascular access site due to lymphangiectasia has been reported during cardiac catheterisation.[232]

Taken together, Noonan syndrome and related disorders are notable for genotype–phenotype relationships such as the associations between *RAF1* and hypertrophic cardiomyopathy and *HRAS* and atrial tachycardia. Bleeding and lymphatic abnormalities may complicate the peri-operative course. Additional peri-operative outcome studies are warranted.

Marfan syndrome and related disorders

Marfan syndrome is present in approximately one in 5000 live births and most commonly caused by mutations in the *FBN1* gene, which encodes the extracellular matrix protein fibrillin-1.[233] Skeletal abnormalities – for example, pectus deformity, long arms, short upper body segment, craniofacial dysmorphism, and arachnodactyly – and ocular abnormalities – such as ectopia lentis and myopia – are often present.[234] Cardiovascular involvement consists of aortopathy, characterised by thoracic aortic aneurysm and risk for dissection, and mitral valve prolapse. Development and intellectual ability are typically normal. Although most patients with Marfan syndrome do not require cardiac surgery until adulthood,[235] excellent operative survival has been demonstrated in children undergoing aortic root replacement.[236–238] Peri-operative providers should recognise risk for pneumothorax and other pulmonary co-morbidities including pulmonary emphysema.[239] Pectus deformity or severe scoliosis may also impact surgical approach and recovery. Some patients with particularly severe cardiovascular disease are referred to as having neonatal Marfan syndrome, which is associated with mutations in exons 24–32 of *FBN1*.[240,241] Arachnodactyly, congenital contractures, and crumpled ears feature prominently in these neonates, who often present with severe mitral and tricuspid valve regurgitation, leading to cardiac failure and death within the first few months of life. Rare cases of surgical success including quadrivalvar replacement and cardiac transplantation have been reported.[242,243]

Loeys–Dietz syndrome, which is associated with mutations in the TGF-β receptor genes *TGFBR1* and *TGFBR2*, has overlapping but distinct phenotypic features with Marfan syndrome.[244] Systemic features include hypertelorism, bifid uvula, cleft palate, craniosynostosis, and velvety/thin skin. Talipes equinovarus and camptodactyly may also be diagnostic clues in a neonate.[245] The major cardiovascular manifestations are generalised arterial tortuosity and risk for aneurysm and dissection. Additional cardiovascular lesions include bicuspid aortic valve, atrial septal defect, and mitral valve prolapse. Vascular disease in Loeys–Dietz syndrome is typically more severe than Marfan syndrome with risk of rapid progression and aortic dissection. Dissection is described as early as 6 months of age.[246] There is also often more extensive arterial involvement, which may require complete aortic replacement. Tortuosity and aneurysm of the brachiocephalic and intra-cranial arteries may predispose to cerebrovascular events.[247,248] Despite the aggressive vascular features of the disease, successful aortic root replacement in infancy has been reported.[249] Furthermore, there were no operative deaths among two series of children with Loeys–Dietz syndrome undergoing aortic root replacement.[246,250] Cardiovascular complications in the setting of complex CHD have included progressive pulmonary artery dilation and rupture and post-operative mitral leaflet rupture.[245,251,252] Similar to Marfan syndrome, patients with Loeys–Dietz syndrome have increased risk of post-operative pneumothorax.[247,250] Careful peri-operative positioning should be utilised due to risk of low bone mineral density and increased fracture risk as well as cervical spine anomalies.[247,253–255] Tortuosity or aneurysm of the peripheral arteries also may impact vascular access.[247]

Taken together, early post-operative outcomes are generally favourable for these conditions, but the risk of recurrent aneurysm or dissection mandates lifelong surveillance. Loeys–Dietz syndrome has unusual characteristics that may not be well recognised due to the more recent discovery and characterisation of the disorder.

Alagille syndrome

Alagille syndrome has a prevalence of at least one in 70,000 live births and is associated with the Notch signaling pathway genes *JAG1* (97% of cases) and *NOTCH2* (1% of cases).[256] The hallmark systemic manifestations include bile duct paucity, resulting in cholestasis, facial dysmorphism – deep-set eyes, prominent ears, triangular face with broad forehead, and pointed chin – vertebral anomalies, and ocular anomalies, often posterior embryotoxon. CHD is present in at least 90% of the cases. The most common cardiovascular findings are right-sided lesions including proximal branch pulmonary artery stenosis, peripheral pulmonary artery stenosis, tetralogy of Fallot, or pulmonary valve stenosis. Left-sided lesions and septal defects are also observed but are less frequent.[257] In addition to the hallmark systemic features, renal anomalies are observed in ~40% of patients, which includes 20% with renal dysplasia and 5% risk of developing chronic renal failure.[258] There is evidence that patients with Alagille syndrome have relatively poor longitudinal outcomes in the setting of tetralogy of Fallot or pulmonary atresia with ventricular septal defect;[257,259] however, positive early outcomes were recently reported among 15 patients with pulmonary atresia and major aortopulmonary collateral arteries[260] and six patients undergoing primary surgical reconstruction of peripheral pulmonary artery stenosis.[181] Owing to congenital biliary anomalies, Alagille syndrome may present the unusual challenge of requiring

paediatric cardiac surgery in patients with severe liver disease; two small case series have reported operative mortality in two out of four children with Alagille syndrome and end-stage liver disease undergoing cardiac surgery.[261,262]

It is increasingly clear that Alagille syndrome is a disorder characterised by diffuse arteriopathy and that arterial anomalies – aneurysm or stenosis – significantly contribute to poor outcomes. In a large cohort of 268 patients with Alagille syndrome, systemic arterial anomalies or intra-cranial vascular events were present in nearly 10% of patients, and vascular accidents were responsible for 34% of the observed mortality.[263] Spontaneous haemorrhage in the gastrointestinal tract, nasal/oral mucosa, and uterine lining are also reported in the absence of liver failure. It is speculated that elevated levels of apolipoprotein E may impair normal haemostasis,[264] but a primary arterial fragility may be likely. A unique case report of a child with recurrent aortopulmonary shunt dehiscence due to extensive atherosclerosis and plaque at the anastomosis site has prompted some to consider routine screening and treatment for dyslipidaemia to prevent exacerbation of arterial disease in these patients.[265] Taken together, systemic arteriopathy presents significant challenges to both early and late survival outcomes.

Trisomy 13 and 18

Patients with trisomy 13 – Patau syndrome – or trisomy 18 – Edwards syndrome – have severe co-morbidities and poor prognosis with >90% of the affected infants dying by age 1 year. Given the severe multi-systemic nature of these disorders, the presence of CHD may not impact overall survival.[266] Cardiac lesions are most commonly septal defects, but left ventricular non-compaction associated with progressive heart failure has been described in trisomy 13.[267,268] Despite poor overall survival, cardiac operations including palliative and complete repairs may be beneficial in select groups.[269,270] The care for these patients and families requires a balanced multidisciplinary approach including palliative care specialists.

CHARGE syndrome

CHARGE syndrome is present in approximately one in 8500 live births.[271] Most cases (~70%) are associated with mutation in the *CHD7* gene, which encodes a chromodomain helicase DNA-binding protein, and are rarely associated with mutation in *SEMA3E*;[272,273] 22q11 deletion has also been described in patients clinically diagnosed with CHARGE syndrome.[274] The major diagnostic criteria (“four C’s”) are coloboma, choanal atresia, cranial nerve dysfunction, and characteristic ear anomalies, external and middle ear anomalies.[275] CHD is present in ~75% of patients and includes conotruncal and septal defects, including atrioventricular septal defects.[272,276] Forebrain central nervous system malformations are frequently observed,[277] yet significant intellectual disability is not guaranteed.[275] Immunological dysfunction including severe T-cell deficiency has been reported.[278] Renal anomalies are observed in ~30–40% cases and include solitary kidney, hydronephrosis, renal hypoplasia, duplex kidneys, and vesicoureteral reflux.[275]

Peri-operative outcomes have not been frequently reported, but sub-optimal longitudinal outcomes for patients with conotruncal defects have been suggested.[31] A major peri-operative risk factor is the high frequency of anatomical and functional abnormalities of the

respiratory tract. Upper airway anomalies – choanal atresia, cleft lip/palate, and micrognathia – and laryngotracheal anomalies – tracheoesophageal fistula, laryngomalacia, tracheomalacia, sub-glottic stenosis, laryngeal cleft, and anterior larynx – may complicate airway management.[279,280] Cranial nerve dysfunction – for example, cranial nerves IX and X – leads to pharyngeal and laryngeal dysfunction and poor airway protection, a problem that may be exacerbated by high frequency of gastroesophageal reflux.[281] Indeed, post-operative airway events are frequently encountered – 35% in a recent series – occurring most frequently after cardiac surgery.[282] In an early case series, over half of deaths were attributed to pulmonary aspiration.[283,284] Pituitary structural abnormalities may be associated with neonatal hypocortisolism and should be considered in cases of refractory hypotension.[285,286]

Rare genetic syndromes associated with CHD have features predisposing to poor perioperative outcomes that may be sub-optimally recognised by providers due to lack of familiarity

Ellis–van Creveld syndrome

Ellis–van Creveld syndrome is a rare autosomal-recessive disorder (*EVC* or *EVC2* mutations) with increased occurrence among the Amish population inhabiting Pennsylvania, United States of America.[287] Frequent characteristics include short stature, polydactyly, short ribs, and dysplastic nails, hair, and teeth. Notably, cognitive development is normal. CHD is present in ~60% and includes common atrium, atrioventricular septal defect, and systemic and pulmonary venous abnormalities.[288,289] Overall, three noteworthy retrospective studies have analysed cardiac surgical outcomes. A case series of nine patients undergoing cardiac surgery at a single centre from 2004 to 2009 observed a preponderance of respiratory morbidity.[288] Death occurred within 150 days after surgery in four out of nine patients, primarily due to respiratory failure. Respiratory complications, including three of five survivors requiring tracheostomy, were attributed to a thoracic dystrophy similar to Jeune syndrome. Increased procedure-related respiratory morbidity was also observed in the Pediatric Health Information System database from 2004 to 2011.[290] In fairly stark contrast with these reports, a review of the Pediatric Cardiac Care Consortium database from 1982 to 2007 identified no operative mortality among 21 children undergoing cardiac surgery.[289] The reason for the discrepancy between these reports is unclear. Notably, thoracic dystrophy may improve with somatic growth, suggesting benefit of deferring surgery for as long as possible.[288] Together, these observations indicate the need for complete pulmonary evaluation and consideration of invasive haemodynamic assessment before cardiac operations.

VACTERL

VACTERL association likely represents a genetically heterogeneous population consisting of vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula with oesophageal atresia, renal anomalies, and limb defects.[291] The renal anomalies include unilateral agenesis, horseshoe kidney, cystic disease, and dysplasia, and there is risk for chronic kidney disease with progression to end-stage renal disease.[292] In a cohort of 46 patients, 31 had

CHD, which was most frequently ventricular septal defect.[293] Probably due to the currently imprecise nature of this diagnosis, there are little outcomes data available.

PHACES

PHACES association includes posterior fossa malformations, haemangioma – often large, segmental, and involving the head or neck – arterial anomalies, cardiac defects, eye abnormalities, and sternal defects.[294] A genetic aetiology has not been established. Arterial manifestations include anomalous patterning, stenosis, occlusion, or aneurysm of the cervical and/or cerebral arteries, which are usually ipsilateral to the haemangioma.[295,296] Aortic arch sidedness is also often ipsilateral to the haemangioma.[297] Cardiovascular malformations are present in ~40% of patients, including aberrant subclavian artery, coarctation of the aorta (~20%), and ventricular septal defect (~15%).[298] Coarctation morphology is often complex and is rarely associated with bicuspid aortic valve.[294] Preparation for surgical repair of coarctation should include a complete evaluation of the aortic arch and head and neck arteries by cardiac catheterisation or other imaging modality to optimise surgical approach.[294,299] Peri-operative providers should also recognise increased risk for subglottic haemangioma and risk for ischaemic stroke and seizures during infancy.[300–302]

Cri du chat syndrome

Cri du chat syndrome (5p15 deletion) has a prevalence of approximately one in 15,000 live births.[303] A distinguishing feature is the characteristic high-pitched cry. Neonatal craniofacial features include microcephaly and round face with large nasal bridge, hypertelorism, and micrognathia. Severe psychomotor and growth delay is observed in most cases. Tracheal intubation may be complicated by the presence of laryngeal abnormalities including small larynx, narrow diamond-shaped larynx, and laryngomalacia, and large, floppy epiglottis.[304] CHD is present in ~ 20% of the patients, including patent ductus arteriosus, ventricular septal defect, atrial septal defect, and right ventricular outflow tract obstructive lesions including tetralogy of Fallot.[305] Outcomes data are limited, but a review of the Pediatric Cardiac Care Consortium from 1982 to 2002 identified 18 children undergoing cardiac surgery, including five complete tetralogy of Fallot repairs, who had good overall survival with one operative death.[305]

Jacobsen syndrome

Jacobsen syndrome has a prevalence of approximately one in 100,000 live births and is associated with a deletion on the long arm of chromosome 11 with break point at 11q23.[306] The pathogenic gene for cardiovascular manifestations may be *ETS1*.[16] Dysmorphic features include skull deformity – for example, trigonocephaly – hypertelorism, strabismus, low posteriorly rotated ears, and syndactyly. Intellectual disability and behavioural abnormalities are observed in the majority of cases. CHD occurs in ~50% of cases, primarily consisting of ventricular septal defect or left-sided obstructive lesion, including up to 5% with hypoplastic left heart syndrome.[307,308] Importantly, there is often increased bleeding risk due to a platelet disorder – Paris–Trousseau syndrome – characterised by neonatal thrombocytopaenia, which can be severe but improves with age, and platelet dysfunction, which often persists.[306,308] Pre-operative evaluation of platelet function using

thromboelastography may be warranted. Airway management can be complicated by micrognathia and anterior laryngeal opening.[309] Central hypothyroidism has been reported.[310] Renal and urinary tract malformations, including dysplasia, hydronephrosis, and unilateral agenesis, occur rarely.[306,307]

Kabuki syndrome

Kabuki syndrome has a prevalence of approximately one in 32,000 live births and in most cases is associated with mutations in the *MLL2* gene, which encodes a histone methyltransferase.[311,312] Its naming is derived from a characteristic appearance of long palpebral fissures with lower eyelid eversion and arched eyebrows, resembling masks worn in Kabuki theatre. Another characteristic finding is foetal finger pads. Intellectual disability is present in ~90% and seizures in 12–25%.[313–315] Cardiac defects are present in ~50% of cases and include ventricular septal defect, atrial septal defect, left-sided obstructive lesions – most commonly coarctation of the aorta – and tetralogy of Fallot.[313,314,316] Abnormalities in humoral immunity, including low levels of IgA, total IgG, or IgG sub-classes, were observed in ~50%, which may explain the predisposition to upper respiratory infections, and potentially impacts peri-operative risk.[317] Cleft lip/palate including sub-mucous clefts occurs in ~50%.[313] Renal abnormalities include renal dysplasia, agenesis, horseshoe kidney, ectopic kidney, and hydronephrosis.[316]

Smith–Magenis syndrome

Smith–Magenis syndrome has a prevalence of approximately one in 25,000 live births[318] and is associated with the deletion of 17p11.2.[318,319] Craniofacial features include broad face with hypertelorism and upslanting eyes, prognathism, low-set ears, cleft lip/palate, and ocular abnormalities.[320] Mild-to-moderate developmental delay is often observed along with characteristic neurobehavioural features such as sleep disturbance with inverted circadian rhythm and predilection for self-injury.[320] CHD is present in ~30–40% and includes ventricular septal defect, atrial septal defect, right-sided lesions including tetralogy of Fallot, and total anomalous pulmonary venous return.[320–322] The cardiovascular risk profile includes predisposition for dyslipidaemia, including hypercholesterolaemia.[323] Post-operative ischaemic stroke in a young adult with premature cerebrovascular atherosclerosis has been reported.[324] Immunoglobulin levels are low in ~20%.[321] Hypothyroidism presents in ~30%.[321] Epileptiform abnormalities are present in ~50%, and clinical seizures develop in ~20–30%.[320,325] Renal and urinary tract anomalies are present in ~15% and include renal dysplasia, small kidney, vesicoureteral reflux, renal agenesis, and ureteral duplication.[320,326]

Wolf–Hirschhorn syndrome

Wolf–Hirschhorn syndrome has a prevalence of approximately one in 20,000 live births and is associated with the deletion of 4p16.3.[327,328] Patients characteristically have the appearance of a “Greek warrior helmet” with high forehead, prominent glabella, and protruding eyes with hypertelorism.[328] Micrognathia, forehead haemangioma, and cleft lip/palate also occur with increased frequency. Severe developmental delay is uniformly observed, and seizures occur in ~90% of individuals starting at a young age.[329] CHD is present in ~50%, most commonly atrial septal defect, pulmonary stenosis, ventricular septal defect, and patent ductus arteriosus, but more complex lesions have been reported.[328,330,331]

Defects in humoral immunity, including common variable immunodeficiency and isolated IgA deficiency, are frequently observed.[332] Renal and urinary tract defects are observed in ~30% and include vesicoureteral reflux, renal agenesis, dysplasia, or hypoplasia, and horseshoe kidney.[328]

Cornelia de Lange syndrome

Cornelia de Lange syndrome, also known as Brachmann–de Lange syndrome, has a prevalence of approximately one in 10,000 live births and is caused by mutations in the *NIPBL, SMC1A*, or *SMC3* genes, which encode gene products involved in the function of cohesin, a protein complex involved in cell division.[333] Patients have consistent craniofacial features including short neck, low posterior hairline, hirsute forehead, arched and confluent eyebrows, and thick and long eyelashes.[334] Mild-to-moderate intellectual disability is frequent.[335] CHD is present in ~30% and includes pulmonary valve stenosis, peripheral pulmonary artery stenosis, atrial septal defect, ventricular septal defect, left-sided obstructive lesions, and tetralogy of Fallot; there is also risk for progressive atrioventricular valve dysplasia.[336,337]

Airway management may be complicated by micrognathia, cleft palate, sub-mucous cleft, short, stiff neck, and restricted mouth opening.[338] Recurrent infections including fungal infections are reported at increased frequency, and humoral deficiency and T-cell abnormalities have been observed.[339] Thrombocytopaenia has been observed in ~20%.[340] Renal and urinary tract anomalies are observed in ~40% of patients and most frequently renal dysplasia, pelvic dilation, and vesicoureteral reflux are observed.[341] Seizures, often partial type, occur in ~25%.[342]

Holt–Oram syndrome

Holt–Oram syndrome, which is characterised by the triad of atrial septal defect, conduction abnormality, and upper limb malformation – most commonly thumb – has a prevalence of approximately one in 100,000 live births and is caused by mutations in the cardiac transcription factor *TBX5*.[343] Cardiac lesions include atrial septal defect, which is most common, ventricular septal defect, and more complex lesions such as conotruncal defects, atrioventricular canal defects, and left-sided obstructive lesions.[343] The most frequent conduction abnormality is atrioventricular block, most commonly first degree, which may be present in the absence of structural CHD.[344] Aside from the risk of atrioventricular block or other conduction disturbances, there are typically no other significant co-morbidities expected to complicate peri-operative care.

Goldenhar syndrome

Goldenhar syndrome, also known as oculo-auriculovertebral spectrum, occurs in up to one in 6000 live births.[345] Although suspected to be due to abnormal development of the first and second branchial arches, the genetic cause is presently unknown; however, 22q11 deletion was recently reported in patients diagnosed with this disorder.[346] The defining features include unilateral microtia, hemifacial microsomia with mandibular hypoplasia, ocular epibulbar dermoid, and cervical vertebral malformations.[347] CHD is present in ~30% of cases and includes conotruncal defects, ventricular septal defect, and atrial septal

defect.[345] Significant craniofacial distortion and cervical vertebral anomalies may complicate airway management.[348] Renal and urinary tract anomalies include ectopic or fused kidneys, renal agenesis, and vesicoureteral reflux.[349]

Conclusion

The impact of a genetic syndrome and associated co-morbidities on the peri-operative course and outcomes cannot be understated (Table 3). Recognising the risk factors particular to specific genetic syndromes has the potential to prevent or ameliorate peri-operative complications and improve short-term and long-term outcomes (Table 2 and Supplementary Table S3). The development of peri-operative management protocols tailored to specific syndromes based on current knowledge may be an effective strategy to achieve these goals. Understanding the cause is essential to elucidate pathogenesis and develop new treatment strategies. As the capability to interrogate and comprehend the genetic basis of CHD improves and clinical availability of genetic testing proliferates, there are increasing opportunities for early diagnosis, risk stratification, genetic counselling, and anticipatory clinical care.[350] We propose that these tasks may be most effectively achieved by the establishment of multi-disciplinary sub-specialty cardiovascular genetics services.

In order to advance peri-operative management, there are present and future needs to integrate registries containing careful phenotyping and clinical outcomes data – for example, Society of Thoracic Surgeons database and Pediatric Heart Network – with registries containing comprehensive genetic data – for example, the Pediatric Cardiac Genomics Consortium.[351,352] There are a limited number of exemplary studies that illustrate the value of performing comprehensive genetic evaluations and specifically reporting not only positive genetic testing results but also negative results to optimise interpretation and generalisability.[31,33] This design may be more challenging to implement in large registries but should be considered for establishment and updating of registries as genetic testing advances. As clinical investigators continue to delineate the clinical significance of genetic diagnoses and apply the evidence to peri-operative care, there is promise for improvement in both short-term and long-term outcomes, such as neurodevelopment, quality of life, and general health into adulthood.[17,18,353]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

None.

Financial Support

This manuscript received no specific grant from any funding agency, commercial, or not-for-profit sectors.

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Table 1

Summary of post-operative mortality and hospital length of stay outcomes among four frequently encountered genetic syndromes.

	Down syndrome		22q11 deletion		Heterotaxy syndrome		Turner syndrome	
Lesion/operation	**Early mortality**	**LOS**	**Early mortality**	**LOS**	**Early mortality**	**LOS**	**Early mortality**	**LOS**
All cardiac surgery	Low[37–39,71,*]	Low[71]	–	–	High[129,130]	High[130]	–	–
Septal defects								
AVSD	Medium[37,39–46,48,**]	Low[42]	–	–	–	–	–	–
VSD	Low[37,41,*]	High[39,65]	–	–	–	–	–	–
SV lesions								
Stage 1 palliation	High[37,39]	–	–	–	High[129]	–	High[25]	–
Stage 2 palliation	High[37,39]	High[39]	–	–	–	–	–	–
Stage 3 palliation	Medium[37,39,50,51]	High[51]	–	–	Medium[124,129]	–	–	–
Conotruncal defects								
Collective	Low[31,33]	–	Medium[31,33,88]	Low[88]	–	–	–	–
TOF	Low[32,37,39,41,49]	High[39]	Low[32,86]	–	–	–	–	–
PA-VSD	–	–	High[91–93]	–	–	–	–	–
IAA or PTA	–	–	Low[87]	High[87]	–	–	–	–
Other								
CoA	Low[37]	–	–	–		–	Low[160]	High[160]
Cardiac transplantation	–	–	–	–	Medium[137,138]	–	–	–
TAPVR	–	–	–	–	Low[134]	–	–	–

AVSD = atrioventricular septal defect; CoA = coarctation of the aorta; IAA = interrupted aortic arch; LOS = length of stay (in-hospital); PA-VSD = pulmonary atresia with ventricular septal defect; PTA = persistent truncus arteriosus; SV = single ventricle; TAPVR = total anomalous pulmonary venous return; TOF = tetralogy of Fallot; and VSD = ventricular septal defect

Classification of risk for poor early post-operative outcomes relative to patients without the syndromic diagnosis (high: studies reviewed only demonstrating increased mortality or LOS, medium: studies demonstrating increased or no difference in mortality or LOS, low: studies demonstrating no difference in mortality or LOS)

*Some studies reported decreased mortality

**Studies reported increased mortality, decreased mortality, and no difference in mortality

Table 2

Classes of risks and suggested peri-operative precautions/actions for specific syndromes.

Class	Syndromes	Actions
Cardiac rhythm	HTX (SND, AV block, tachyarrhythmia), WS (LQT, ventricular ectopy), TS (LQT), Costello (atrial tachycardia), Holt–Oram (AV block)	Maintenance of normal electrolyte levels, routine placement of temporary pacing wires
Vascular (systemic)	TS, WS, LDS, PHACES	Pre-operative vascular imaging studies, documentation of pre-operative BP, patient-specific BP goals, ultrasound-guided arterial access
Vascular (pulmonary)	DS, HTX, EVC	Pre-operative cardiac catheterisation, post-operative manoeuvers to minimise PVR
Myocardial	HTX (non-compaction cardiomyopathy), trisomy 13 (non-compaction cardiomyopathy)	Intra-operative myocardial protection, anticipatory post-CPB management of ventricular dysfunction
Respiratory	Upper airway anomalies: DS, 22q11 deletion, CHARGE, PHACES, Cri du chat, Cornelia de Lange Lower airway disease: DS, EVC, MFS/LDS	Pre-operative anatomic upper airway evaluation, extubation protocols, post-operative evaluation of airway protection mechanisms, otolaryngology/ pulmonary consultation
Immunologic/infectious	DS, 22q11 deletion, HTX, Kabuki, Smith–Magenis, Wolf–Hirschhorn, Cornelia de Lange	Immunology consultation, broad-spectrum antimicrobial prophylaxis, minimise invasive monitoring
Haematologic	22q11 deletion, NS, AGS, Jacobsen, Cornelia de Lange	Haematology consultation, post-CPB antifibrinolytics, BP control, rapid access to blood products, liberal blood product administration
Neurologic	Seizure: DS, 22q11 deletion, Kabuki, Smith–Magenis, Wolf–Hirschhorn	Seizure: neuroprotection, peri-operative EEG evaluation, normocalcaemia (22q11 deletion)
	Cerebrovascular: AGS, PHACES, LDS, WS, NS Cervical instability: DS, LDS	Cerebrovascular: pre-operative cerebrovascular imaging, cerebral perfusion pressure monitoring, urgent imaging for neurological changes Cervical instability: appropriate positioning/support
Endocrine	Hypothyroidism: DS, TS, WS, PHACES, Jacobsen, Smith–Magenis Pituitary dysfunction: CHARGE	Pre-operative thyroid function testing, endocrinology consultation as needed, steroid replacement
Lymphatic	DS, TS, NS	Monitoring for chylothorax and sequelae if present, early transition to low and medium chain triglyceride diet/ formula, minimise central venous pressure

AGS = Alagille syndrome; AV = atrioventricular; BP = blood pressure; CPB = cardiopulmonary bypass; DS = Down syndrome; EEG = electroencephalogram; EVC = Ellis–van Creveld; HTX = heterotaxy syndrome; LDS = Loeys–Dietz syndrome; LQT = prolonged QT interval; MFS = Marfan syndrome; NS = Noonan syndrome; PVR = pulmonary vascular resistance; SND = sinus node dysfunction; TS = Turner syndrome; and WS = Williams syndrome

Table 3

Key points.

Genetic syndromes often present specific cardiovascular and non-cardiovascular co-morbidities that negatively impact mortality and morbidity outcomes
Diagnosis of a genetic syndrome allows for risk stratification, counseling on prognosis and recurrence risk, anticipatory peri-operative management, and therapy decisions
Syndrome-specific protocols for peri-operative evaluation and prophylactic tactics may improve peri-operative outcomes. Particular attention should be given to immunological, haematological, vascular, and neurological risks. Cardiac anaesthesia during non-cardiac procedures should be considered in the context of certain genetic syndromes
Improved peri-operative outcomes may translate to improved short-term and long-term outcomes and reduce long-term co-morbities and cost
Design and reporting of surgical database registries and clinical trials should clearly define diagnostic criteria for genetic syndromes and specify positive and negative genetic testing results
Integration of large clinical and genetic databases will advance clinical outcomes
The development of cardiovascular genetics services will provide sub-specialty expertise on specific aspects of care of patients with genetic diagnoses, which over time will be increasingly encountered