Perioperative Management of Patients With DiGeorge Syndrome Undergoing Cardiac Surgery

Tze Yeng Yeoh, MB, ChB,*† Federica Scavonetto, MD,* Ryan J. Hamlin, MD,* Harold M. Burkhart, MD,‡ Juraj Sprung, MD, PhD,* and Toby N. Weingarten, MD*

Objective: **DiGeorge syndrome is a genetic disorder with multisystem involvement resulting in craniofacial and cardiac anomalies and parathyroid and immune system dysfunction. This study describes perioperative management of a large cohort of patients with DiGeorge syndrome undergoing cardiac surgery.**

Design: **Retrospective cohort study.**

Setting: **Major academic tertiary institution.**

Participants: **The medical records of patients diagnosed with DiGeorge syndrome and undergoing cardiac surgery at this institution, from January 1, 1976, to July 31, 2012, were reviewed for phenotypic characteristics and intraoperative and postoperative complications, with specific attention to hemodynamic instability, perioperative perturbations of plasma calcium homeostasis, and airway difficulty.**

Interventions: **None.**

Measurements and Main Results: **Sixty-two patients underwent 136 cardiac surgical procedures; 47 patients (76%) had multiple operations. Sternotomies for reoperations often were complex (8 complicated by vascular injury or difficulty achieving hemostasis and 5 requiring bypass before sternotomy). Two patients had persistent hypocalcemia intraoperatively, requiring infusion of calcium chloride, and hypocalcemia developed postoperatively in 8 patients. Prolonged mechanical ventilation (>24 hours) was required after 48 procedures (35%), and 25 (18%) required prolonged inotropic support (>72 hours). Infectious complications occurred after 31 procedures (23%). There was no in-hospital or 30-day mortality.**

Conclusions: **Patients with DiGeorge syndrome often have complex cardiac anomalies that require surgical repair. The postoperative course is notable for the frequent need for prolonged respiratory and hemodynamic support. Patients can develop hypocalcemia and may require calcium supplementation. Immunodeficiencies may be associated with the increased rate of postoperative infections and may dictate the need for specific transfusion management practices.**

KEY WORDS: anesthesia, cardiovascular surgical procedures, DiGeorge syndrome, hypocalcemia, immunosuppression, infection

DIGEORGE SYNDROME (DGS), or 22q11.2 deletion syndrome, is a multisystem disorder associated with congenital heart disease, craniofacial abnormalities, developmental delays, and disorders of the endocrine, immune, and hematologic systems.[1,2] It is inherited in an autosomal dominant fashion, but most deletions (>90%) occur as a de novo mutation.[3] Patients typically have cyanotic heart disease secondary to conotruncal heart defects (malformations of the cardiac outflow tracts) such as tetralogy of Fallot, pulmonary atresia with ventricular septal defect, truncus arteriosus, interrupted aortic arch, and ventricular septal defect.[4]

Only a few reports have been published describing the perioperative management of patients with DGS undergoing surgical repair of congenital cardiac anomalies.[4–10] Because this syndrome is uncommon, case series and case reports are required to provide information regarding perioperative challenges in the management of patients with DGS. This institution has long experience in caring for patients with congenital heart disease and a comparatively large number of DGS patients who have undergone cardiac surgery. The aim of this study was to report the perioperative course of patients with DGS who had had cardiac surgery for congenital abnormalities at this large tertiary center.

METHODS

This retrospective medical record review received approval from the Institutional Review Board. The authors included only patients who provided authorization for research use of their medical records (historically >95% of the patients).[11] This research was conducted in compliance with the World Medical Association Declaration of Helsinki.

A computerized search of medical record databases at this institution, from January 1, 1976, to July 31, 2012, was conducted to identify all patients with a genetic or clinical diagnosis of DGS. The records of identified patients were reviewed further to identify those who underwent cardiac surgery at this institution (charts reviewed by TY, FS, and RJH). Patients who underwent cardiac surgery at another institution were not included. Patients who underwent minor cardiac surgical procedures such as cardiac catheterization (both diagnostic and interventional) and insertion of pacemakers under sedation were not included. However, those who underwent placement of pacemakers or implantable cardioverter-defibrillators with epicardial leads that required a sternotomy or thoracotomy under general anesthesia were included.

The genetic diagnosis of DGS was made with the fluorescent in situ hybridization test to identify deletions on chromosome 22q11.2.[12,13] All clinical diagnoses were made by a staff physician specialist in pediatrics, pediatric cardiology, or genetic medicine on the basis of phenotypic characteristics, family history, and presence of multiple congenital heart malformations.

Medical records were reviewed for phenotypic characteristics of DGS: Congenital cardiovascular, craniofacial, and airway anomalies; disorders of the immune, endocrine, gastrointestinal, genitourinary, neurologic, ophthalmologic, skeletal, and hematologic systems; developmental and neuropsychiatric abnormalities; and other comorbid conditions unrelated to DGS. Surgical and anesthetic records were reviewed for intraoperative events such as difficult airway management,

*From *Department of Anesthesiology, Mayo Clinic, Rochester, MN; †Department of Anaesthesia, National University Hospital, National University Health System, Republic of Singapore; ‡Division of Cardiovascular Surgery, Mayo Clinic, Rochester, MN.*

Address correspondence and reprint requests to Toby N. Weingarten, MD, Department of Anesthesiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Fax: +507 255 6463. E-mail: weingarten.toby@mayo.edu

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blood transfusions, interventions to provide hemodynamic support such as inotropic infusions or mechanical interventions such as intra-aortic balloon pump or extracorporeal membrane oxygenation, hypocalcemia, arrhythmias requiring interventions, and specific documentation of difficulty achieving hemostasis or inadvertent vessel injury. Hospital records were reviewed for postoperative complications. Reflecting the typical surgical practice with pediatric cardiac patients, prolonged ventilation was defined as requiring mechanical ventilation for more than 24 postoperative hours and prolonged inotropic support was defined when being extended beyond 72 postoperative hours. Infections were defined as fever (temperature $>38^{\circ}C$); treatment with antibiotics; and positive blood, respiratory, or urine cultures. However, isolated sternal wound infections were considered as infectious complications even if not accompanied by fever.

Descriptive summaries of demographic, epidemiologic, and perioperative complications and other data were performed and are reported as medians or frequencies (percentages). Because of the prolonged timespan of this study, additional analysis was performed comparing outcomes of surgeries performed during the early (before the year 2000) and later epoch (year 2000 and after) in regard to duration of postoperative mechanical ventilation, inotropic support, and intensive care unit days. The frequency of infections between the two epochs also was compared.

To review the current knowledge regarding anesthetic complications in patients with DGS undergoing cardiac surgery, the authors performed a literature search of MEDLINE (January 1, 1946 to July 31, 2012) and EMBASE (January 1, 1988 to July 31, 2012) databases using the following text words: *22q11 deletion syndrome* or *DiGeorge syndrome*, *anesthesia*, *anesthetics*, *intraoperative*, *preoperative*, and *postoperative*. Published articles and selected bibliographies were reviewed for relevancy.

RESULTS

One hundred thirty-one patients with DGS were evaluated at this institution from January 1, 1976, to July 31, 2012. Of these, 62 patients underwent 136 cardiac surgical procedures. Of these, 64 cases (47%) were performed in the contemporary epoch (2000 or later) and 72 (53%) cases in the early epoch (47 cases during the 1990s, 25 cases before 1990). From 2000 to 2012 there were 33,119 cardiac surgeries; thus, DGS cardiac surgical patients accounted for 0.2% of the contemporary practice. Characteristics and comorbid conditions of patients in this cohort are summarized in Table 1. Diagnosis of DGS was made before the first cardiac surgery in 18 (29%) patients and after the first cardiac surgery in 44 (71%) patients. Fifty-six patients (90%) had cyanotic conotruncal heart abnormalities, and 47 patients (76%) had multiple cardiac surgical procedures. Other congenital anomalies were common.

Surgical characteristics and intraoperative complications are summarized in Table 2. The three most common surgical procedures were systemic-to-pulmonary shunts, valvular operations, and unifocalization procedures (reincorporation of the aortopulmonary collaterals into the pulmonary vasculature for treatment of pulmonary atresia). Ninety-one procedures were performed using cardiopulmonary bypass. All patients were weaned from cardiopulmonary bypass. However, one patient who underwent repair of pulmonary atresia required a return to bypass for reopening of a ventricular septal defect because of persistently high right ventricular pressure. Six patients underwent eight procedures with difficulty achieving hemostasis and/or inadvertent vessel injury during sternotomy. None of these

Table 1. Characteristics and Comorbid Conditions in Patients with DiGeorge Syndrome

Patient Characteristics and Comorbid Conditions	Total Patients (N = 62)
Male sex	32 (52)
ASA status ≥3	62 (100)
Diagnosis	
Genetic	60 (96.8)
Phenotypic	2 (3.2)
Age at diagnosis, y[*]	2 (0.1-14)
Age at first cardiac surgery at this institution, y	1 (0.2-7)
Cardiovascular disease	62 (100)
Cyanotic heart disease	
Tetralogy of Fallot	16
Pulmonary atresia and VSD	21
Pulmonary stenosis and VSD	5
Truncus arteriosus	4
Interrupted aortic arch or coarctation of the aorta	8
Atrioventricular canal defect	1
Double-outlet right ventricle, pulmonary stenosis, VSD	1
Acyanotic heart disease	
VSD, ASD, PDA	6
Valvular heart disease	5
Vascular ring or major arterial malformations (aortic arch, anomalous subclavian, carotid)	17
Airway and ear, nose, and throat disease	32 (52)
Velopharyngeal incompetence or insufficiency	9
Upper airway anomalies[†]	9
Laryngomalacia, tracheomalacia, or bronchomalacia	3
Recurrent acute otitis media or chronic otitis media	19
Micrognathia or retrognathia	1
Hearing loss (sensorineural, conductive, or mixed)	10
Immune-related disease	21 (34)
Recurrent infections (UTI, pneumonia, URTI)	14
Low T-cell count or impaired function	7
Autoimmune diseases[‡]	5
Immunoglobulin deficiency	3
Absent thymus or thymic hypoplasia	3[§]
Endocrine disease	29 (47)
Hypocalcemia with or without hypoparathyroidism	24
Thyroid disorders	9
Gastrointestinal disease	15 (24)
Gastroesophageal reflux disease	11
Dysmotility or dysphagia	6
Hernia (umbilical, inguinal, or diaphragmatic)	3
Genitourinary disease	3 (5)
Unilateral renal agenesis or unilateral absent kidney/congenital hydronephrosis	3
Vesicoureteral reflux	1
Ophthalmic disease	9 (15)
Strabismus	4
Refractory errors or astigmatism	5
Musculoskeletal disease	13 (21)
Scoliosis or other spine anomalies	13
Microcephaly and plagiocephaly	1
Hematologic disease	8 (13)
Thrombocytopenia	8
Neurologic disease	6 (10)
Recurrent seizures (>1 episode) (with or without hypocalcemia)	6

Table 1 (*continued*)

Patient Characteristics and Comorbid Conditions	Total Patients (N = 62)
Growth and development	33 (53)
Developmental delay	31
Speech and language delay	15
Neuropsychiatric disease	13 (21)

NOTE. Data presented are number of patients (percentage) or median (25th-75th percentile).

Abbreviations: ASA, American Society of Anesthesiologists Physical Status; ASD, atrial septal defect; PDA, patent ductus arteriosus; URTI, upper respiratory tract infection; UTI, urinary tract infection; VSD, ventricular septal defect; y, years.

*Age not available for 25 patients.

†Includes cleft lip, cleft palate, submucous cleft palate, anterior glottic web, or subglottic stenosis.

‡Includes juvenile rheumatoid arthritis, psoriatic arthritis, psoriasis, and idiopathic thrombocytopenia purpura.

§Two patients had an absent thymus, and 1 patient had thymic hypoplasia.

patients had presurgical thrombocytopenia or other coagulopathies, but all had multiple prior sternotomies. Femoral cannulation and the initiation of cardiopulmonary bypass were performed prophylactically in 2 patients before repeat sternotomies. Three other patients undergoing repeat sternotomies underwent emergent femoral cannulation and the initiation of cardiopulmonary bypass because of bleeding (acute arterial bleeding (n = 2) or innominate vein laceration (n = 1). Two patients required calcium chloride infusions for 3 procedures. One patient, a 1-month-old child, during a type-B interrupted arch repair was found to have hypocalcemia, which did not correct with repeated boluses of calcium chloride. An infusion of calcium chloride was initiated and continued for 3 days until enteral feeding began. During this period the child had a second surgery for closure of the sternum. The second patient was a 5-month-old child undergoing tetralogy of Fallot repair. Hypocalcemia was diagnosed while the patient was hypotensive, requiring an infusion of dobutamine, epinephrine, and phenylephrine. An infusion of calcium chloride was initiated and hemodynamics improved. The infusion was continued for the first postoperative day. Fifty-nine (95%) patients were intubated on the first attempt; the remaining 3 patients had Cormack-Lehane grade IIa or IIb view[14] and were intubated successfully with direct laryngoscopy within 3 attempts.

The postoperative course is summarized in Table 3. Prolonged mechanical ventilation was required after 48 surgical procedures (35%); 26 patients (19%) required intubation longer than 72 hours; and 16 patients (12%) after extubation required tracheal reintubation, including 14 patients within 12 hours from extubation. Three patients required tracheotomies because of acute airway compromise from sternal wound hematoma, subglottic stenosis, and after multiple failed extubation attempts in the setting of congestive heart failure. Prolonged inotropic support was required after 25 procedures (18%). Hypocalcemia requiring replacement developed in 8 patients, with 1 patient developing seizures. Of the 10 patients who had persistent hypocalcemia (both intraoperative and postoperative), 4 were not yet diagnosed with DGS and 3 had normal parathyroid

Table 2. Surgical Characteristics and Intraoperative Complications of Patients with DiGeorge Syndrome Who Underwent Cardiac Surgical Procedures

Surgical Procedures or Events	No. (%)
No. of surgical procedures	136
Elective surgery	134*
Age at time of surgery	
<1 month	10 (7.4)
1 month to 1 year	21 (15.4)
1 to 5 years	45 (33.1)
6 to 12 years	27 (19.9)
13 to 18 years	20 (14.7)
>18 years	13 (9.6)
Type of surgery	
Sternotomy	38 (27.9)
Primary	38 (27.9)
Re-entry	93 (68.4)
None	5 (3.7)
Cardiopulmonary bypass	91 (66.9)
Corrective surgery	41 (30)
Complete repair of TOF	7
Complete repair of pulmonary atresia and VSD	9
Complete repair of AV canal defect	1
Complete repair of truncus arteriosus	3
Complete repair of interrupted aortic arch	4
Resection of subvalvular pulmonary stenosis, closure of PFO and VSD	1
Closure of VSD, ASD, PFO, or PDA ligation	12
Division of vascular ring	4
Palliative surgery	53 (39)
Systemic-to-pulmonary shunt†	21
Unifocalization procedure	16
Norwood procedure	1
Fontan procedure and repair of tricuspid valve	1
Pulmonary artery banding	1
Reconstruction of right ventricular outflow tract with or without pulmonary valve replacement	10
Patch augmentation of pulmonary arteries	1
Pulmonary valvotomy or valvectomy	2
Valvular surgery	36 (27)
Conduit or homograft replacement	19
Aortic or pulmonary valve replacement or repair	14
Mitral or tricuspid valve replacement or repair	3
Other procedures	6 (4)
Insertion of pacemaker or ICD	3
Miscellaneous‡	3
Intraoperative complications	
Difficult intubation	3
Reactive airways disease requiring treatment	1
Arrhythmias requiring electroconversion, pacing, and/or medications§	3
Hypotension requiring inotropic support§	16
Events coming off bypass	
Requiring inotropic support	68 (74.7)‖
Requiring intra-aortic balloon pump or ECMO	0
Requiring nitric oxide	2 (2.2)‖
Arrhythmias requiring countershock, pacing, and/or medications	17 (18.7)‖
Return to bypass to reopen the VSD because of high right ventricular pressure	1 (1.1)‖
Bleeding	
Requiring RBCs, FFP, platelets, and/or cryoprecipitate	90
Difficult hemostasis or inadvertent arteriotomy/venotomy during sternotomy	8

Table 2 (*continued*)

Surgical Procedures or Events	No. (%)
Reoperation	
Delayed sternal closure	7
Persistent bleeding	2
Miscellaneous complications	
Persistent hypocalcemia requiring calcium chloride infusion	3
Iatrogenic femoral artery injury from inadvertent insertion of central line	1
Duration of surgery, min	213 (155-255)
Bypass time, min	82 (60-111)
Aortic cross-clamp time, min	48 (26-66)
Total circulatory arrest time, min	23 (15-35)
Transfusion	51

NOTE. Data presented as number of surgical procedures (percentage), number of events, or median (interquartile range).

Abbreviations: ASD, atrial septal defect; AV, atrioventricular; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; ICD, implantable cardioverter-defibrillator; min, minutes; PDA, patent ductus arteriosus; PFO, patent foramen ovale; RBC, red blood cell; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

*The two emergency surgeries occurred in the same patient. At 22 days of age he underwent emergent pulmonary valvectomy for severe pulmonary stenosis. At 4 years of age he underwent pulmonary artery dilation and stent placement. This was complicated by stent thrombosis and he underwent surgical removal of the stent.

†Modified left Blalock-Taussig shunt, modified right Blalock-Taussig shunt, ascending aorta-to-pulmonary artery shunt, and bidirectional caval pulmonary shunt.

‡Suture closure of dehisced mitral cleft, pericardiectomy, exploratory median sternotomy to further define cardiac anatomy.

§Cardiac surgeries that do not require bypass or events that occurred before bypass.

‖Percentages calculated using the number of cases that required cardiopulmonary bypass as the denominator (N = 91).

hormone levels. One patient needed calcium replacement for more than 1 year. Postoperative seizures occurred in 7 patients, including 1 related to hypocalcemia. Twenty-four procedures (18%) were complicated by postoperative infections such as pneumonia, bacterial tracheitis, urinary tract infection, and septicemia. Additionally, there were 6 sternal wound infections. There were no in-hospital or 30-day deaths.

Comparisons of outcomes of procedures between the early and contemporary epoch found that median days (25th, 75th percentile) of postoperative mechanical ventilation were 1 (1, 2) versus 1 (1, 3), $p = 0.87$, early versus late, respectively; inotropic support was 2 (1, 3) versus 2 (1, 3), $p = 0.26$; intensive care unit stay was 3 (2.8, 5) versus 3 (2, 6), $p = 0.69$; and rates of infection 15 (21%) versus 16 (25%), $p = 0.54$. There was a decrease in median cardiopulmonary bypass time: 91.5 minutes (66, 148) versus 79 minutes (51, 99), $p = 0.02$.

DISCUSSION

This cohort of 62 patients with DGS underwent repairs of complex cardiac anomalies that required long cardiopulmonary bypass time. Often these patients had extracardiac anomalies such as craniofacial abnormalities, parathyroid dysfunction, and immunocompromise, all of which can contribute to perioperative morbidity and mortality.[2,15] A sizeable portion of this cohort required prolonged postoperative mechanical ventilation and inotropic support, and several patients who initially were extubated required subsequent reintubation and mechanical ventilation. Despite these difficulties, there were no in-hospital or 30-day deaths. However, whether the risk of perioperative complications during congenital surgery differs when comparing patients with DGS to patients without DGS but with comparable cardiac anomalies cannot be determined from the design of the present study.

The literature research identified 3 case reports[5,8,10] and 3 case series[6,7,9] of patients with DGS undergoing cardiac surgery. The 3 case reports describe perioperative management complicated by hypocalcemia.[5,8,10] Kyburz et al[6] reported 40 patients and Marmon et al[7] reported 10 DGS patients who underwent cardiac surgery. Simsic et al[9] reported cardiac surgery in 93 neonates, of whom 23 had DGS. These 3 case series[6,7,9] described high rates of postoperative complications related to cardiac failure, respiratory complications, and infectious complications. These results are most similar to those of Kyburz et al,[6] which may reflect that their study encompassed a similar time frame (1978-2003) to this study and that neither cohort was limited to neonates. The series of neonates undergoing cardiac surgery reported by Simsic et al[9] had low mortality rates; however, the complication rates were highest among patients with DGS (83%).[9] The high mortality rate of 80% observed by Marmon et al[7] may reflect results from an earlier clinical era (1963-1983) and that the cohort was limited to neonates.

Patients with DGS have complicated heart defects that require complex surgical repairs. Factors that can further complicate cardiac surgery, as evidenced by this cohort, are cardiovascular anomalies of the aortic arch (isolated or involving subclavian artery or arteries) and the pulmonary arterial tree (underdevelopment or hypoplasia of pulmonary arteries and/or major aortopulmonary collateral arteries).[4] Surgical management can be either palliative or corrective. However, even after undergoing corrective surgery, many patients require reoperation for conduit or homograft replacement secondary to patient growth and conduit stenosis and valve replacement or repair because of valvular insufficiency.[6] Ten of the patients (16%) were not suitable candidates for corrective surgical procedures because of poor pulmonary arterial morphology or complex pulmonary atresia. Because these patients often have multiple cardiac surgeries, repeated sternotomies may be complex and lead to inadvertent vessel injury. Some patients may require cardiopulmonary bypass to allow for completion of sternotomy, as was evidenced in 5 of the patients.

The postoperative course of the patients reflected the complexity of surgery; many required prolonged mechanical ventilation and inotropic support, and several required reintubation and tracheotomy. Generally, patients with DGS are at increased risk for recurrent bacterial and viral infections and bronchomalacia.[16] In the series reported by Kyburz et al,[6] 14% of DGS patients undergoing cardiac surgery required postoperative tracheotomy. Simsic et al[9] compared the short-term outcomes after cardiac surgery between neonates with DGS and those without genetic abnormalities and found the neonates with DGS had longer mechanical ventilation time (mean, 10 *v* 8 days), longer stay in the intensive care unit (mean, 16 *v* 10

Table 3. Postoperative Complications in Patients with DiGeorge Syndrome

Postoperative Complications	Events
Respiratory	
Prolonged ventilator support*	48 (35.3)
Tracheal reintubation†	16 (11.8)
Other respiratory complications	
Tracheotomy	3
Reactive airway disease, excessive pulmonary secretions, atelectasis requiring chest physiotherapy, pulmonary toilet, and medications	27
Pneumothorax	3
Intrapulmonary hemorrhage	1
Left hemidiaphragm paralysis	1
Need for noninvasive ventilation after tracheal extubation	9
Cardiovascular	
Arrrhythmias (supraventricular tachycardia, heart blocks, bradycardia)	11
Pulmonary edema or congestive heart failure	10
Pulmonary hypertension or pulmonary over-reactivity requiring nitric oxide	8
Hypotension with reinitiation of inotropic support with or without fluid boluses	3
Endocrine	
Hypothyroid	1
Hypocalcemia	13
Hyponatremia requiring treatment with oral sodium chloride	1
Immunology	
Infections	31
Respiratory	17
Sternal	6
Pericarditis	1
Other	7
Hematology	
Bleeding requiring reoperation and/or transfusion	2
Thrombocytopenia	7
Neurology	
Seizures with or without hypocalcemia‡	7
Embolic stroke	2
Subarachnoid hematoma	1
Gastrointestinal	
Feeding intolerance caused by ileus, reflux, fatigue	9
Bleeding secondary to gastric ulcer, gastritis, or duodenitis	2
Death	
During hospitalization	0
Within 30 d of discharge	0
Ventilator time, d	1 (0-34)
Mechanical ventilation >24 postoperative hours	48 (35)
Inotropic support >72 postoperative hours	25 (18)
ICU length of stay, d	3 (0-85)
Length of stay, d	8 (5-11)

NOTE. Data presented as number of events (percentage) or median (range) for nonparametric variables.

Abbreviations: d, days; ICU, intensive care unit.

*Reasons for prolonged ventilator support included increased airway secretion, atelectasis, or pneumonia (N = 24); hemodynamic instability from pulmonary hypertension requiring nitric oxide, pulmonary edema, and prolonged inotropic support (N = 11 patients); delayed sternal closure (N = 7); seizures (N = 3); coagulopathy (N = 2); intrapulmonary hemorrhage (N = 1).

†Reasons for tracheal reintubation included respiratory failure secondary to atelectasis, trouble to clear secretions, or increased work of breathing (N = 14); seizures (N = 2).

‡Three patients had myoclonic jerks, 1 patient had tonic-clonic seizures, and 3 patients had no documentation on the type of seizure; 1 patient had a seizure in the setting of hypocalcemia.

days), longer hospitalization (mean, 32 *v* 20 days), and higher incidence of complications (83% *v* 51%). The present results cannot be compared directly with those of Simsic et al[9] because the present series was not limited only to neonatal patients, a population in whom the acuity of the cardiac condition is much higher.

Patients with DGS commonly have underdeveloped parathyroid glands, which can result in hypocalcemia.[17] Hypocalcemia in these patients undergoing cardiac surgery has been associated with hemodynamic instability and postoperative seizures.[5,8,10] One of the patients had a seizure clearly related to hypocalcemia. However, these patients do have high rates of seizure disorders that can be independent of hypocalcemia.[18]

Parathyroid function often improves within the first year of life because existing parathyroid tissue can hypertrophy, allowing for normocalcemia.[19] However, these patients may have latent hypoparathyroidism, a decreased parathyroid hormone response to physiologic stress that can progress to overt hypocalcemic hypoparathyroidism.[17,20] Latent hypoparathyroidism was found in 14 of 22 patients with conotruncal cardiac defects undergoing cardiac surgery who required cardiopulmonary bypass, and 4 of these patients had DGS. Schaan et al[8] described a 1.5-year-old girl who, after uneventful surgical correction of tetralogy of Fallot, experienced hypocalcemia and was found to have latent hypoparathyroidism, which persisted for months. In the present cohort, several patients may have had possible latent hypoparathyroidism with normal preoperative parathyroid and calcium levels who developed postoperative hypocalcemia. Because of the constant changes in calcium homeostasis and reduced parathyroid hormone reserves in these patients, it is important to monitor the serum calcium levels in the perioperative period. Endocrinologist consultation is warranted for patients with persistent hypocalcemia.[1] Respiratory alkalosis can lower serum ionized calcium levels and should be avoided.

Craniofacial abnormalities seen in DGS, such as micrognathia, retrognathia, and cleft palate, may theoretically lead to difficult intubation.[5,21] However, in this patient series endotracheal intubation was straightforward and only moderate difficulty was encountered in 3 patients who required several attempts with direct laryngoscopy; intubation did not require fiberoptic intubation. This rate (5%) is somewhat greater than 1.35% rate of difficult intubation reported in pediatric patients undergoing cardiac surgery; however, the authors defined this as Cormack-Lehane grade $\geq$ III,[22] which was a higher grade than encountered with these patients.

Thymic hypoplasia is common in patients with DGS, with approximately 80% having diminished peripheral T-cell counts.[23] True thymic aplasia with absent T cells is rare, occurring in less than 0.5% of DGS patients.[24] Immune function often improves with age, generally by the age of 2 years.[25] Thymic size may correlate poorly with T-cell counts, suggesting extrathymic sources of T-cell production.[26] Two patients in this cohort had an absent thymus but normal immunologic function. Deficiencies in IgG, IgM, or IgA occur in about 10% of DGS patients.[24]

Patients ideally should have preoperative immunologic evaluation that includes flow cytometry, T-cell function, and immunoglobulin determinations, because results can dictate specific transfusion requirements, such as with IgA deficiencies. Because patients may be immunodeficient, only irradiated cellular blood products should be used to prevent transfusion-associated graft versus host disease.[27] In addition, cytomegalovirus-seronegative or leukocyte-depleted blood components should be used to prevent transfusion-transmitted cytomegalovirus infection.[28] One patient in this cohort had a selective IgA deficiency and previous anaphylactic reaction to platelet transfusion that was attributed to IgA deficiency. In preparation for subsequent surgical procedures, she required irradiated blood products as well as blood products that were IgA deficient and washed. In addition, she was premedicated with corticosteroids, antihistamines, and acetaminophen. Cardiac surgical patients with DGS have greater mean platelet volume (10.9 fL *v* 8.6 fL, $p < 0.001$) than other pediatric cardiac surgical patients (mean platelet volume $>$ 10.0 fL has a sensitivity of 80.0% and specificity of 89.7%), which can guide selection of blood products for patients who urgently need a blood transfusion but in whom the diagnosis of DGS is suspected but not confirmed.[15]

Postoperative infectious complications can be common and severe. Marmon et al[7] described 10 neonatal patients who had cardiac surgery, 8 of whom died postoperatively, 6 due to sepsis. Kyburz et al[6] described 40 patients who underwent cardiac surgery; 18 patients had relevant postoperative infections (tracheitis, sepsis, endocarditis, pneumonia, meningitis). In this series, postoperative infections were common and included pneumonia, bacterial tracheitis, otitis media, and urinary tract infections. All but 1 case responded to antibiotic therapy. This patient had low T-cell and B-cell counts and IgG and IgM deficiencies and required intravenous immunoglobulin in addition to antibiotic therapy to treat postoperative pneumonia, urinary tract infection, and otitis media. The improvement in survival observed by Kyburz et al[6] and this series compared with Marmon et al,[7] which represented an earlier era, probably reflects improvement in the perioperative care of congenital cardiac surgical patients. Another difference is that Marmon et al[7] series included only neonates, whereas these patients were generally older children, which can influence the rates of complications. In light of this increased propensity for development of infections, it is critical to practice strict aseptic precautions in all procedures, including placement of a peripheral intravenous catheter or injection of medication into a port of a preexisting catheter. Some patients may be on specific prophylactic antibiotic therapy, which should be continued perioperatively in addition to appropriate prophylaxis indicated by type of surgical procedure. However, in general, the contemporary antimicrobial prophylaxis regimen in these patients is consistent with general surgical practice, with preincisional administrations of an antibiotic with gram-positive coverage (in this institution specifically, cefazolin 25 mg/kg or vancomycin for patients with allergies to beta-lactam antibiotics).

This case series had all the inherent limitations of a retrospective observational study. A major limitation was the long duration of the study period, with possibility of substantial practice changes in the management of congenital cardiac surgery patients. However, the combination of congenital heart disease and DGS is relatively uncommon, thus case reports and

case series are important to help assessing the perioperative management (risk) for these patients. Therefore, the authors felt it of value to expand the duration of the study to provide a greater number of cases. The authors also performed additional analysis comparing outcomes from the contemporary with early epoch and found outcomes did not vary. This lack of improvement in regard to length of mechanical ventilation, inotropic support, intensive care unit duration, and rate of infections may be due to the increasing complexity of patients in the later era. For example, there were changes in the types of procedures performed in the early and later eras. This case series focused on patients with DGS undergoing cardiac surgery, and the authors have not considered other noncardiac operations. Furthermore, besides disease-specific propensity for hypocalcemia, the perioperative complications in children with DGS are consistent with major cardiac operations in patients with congenital heart disease. This study cannot differentiate whether the perioperative course in DGS patients differs from other patients who underwent repair of comparable congenital cardiac malformations. Further, because this study reported outcomes from a clinical practice, many aspects of care did not follow a formal protocol but were dependent on the clinical judgment of the health care team. For example, there is not in place a formal protocol for the measurements of serum calcium concentrations; therefore, mild cases of hypocalcemia may not have been recognized. Finally, this cohort reflects the experience of a major academic tertiary institution with considerable expertise in management of these patients.

CONCLUSION

Cardiac surgical patients with DGS often have complex cardiac anomalies that require complicated surgical repair. The postoperative course is notable for the common need for prolonged respiratory and hemodynamic support. These patients may develop recalcitrant perioperative hypocalcemia, which can be attributed both to the stress of surgery and to latent hypoparathyroidism. Immunodeficiencies may complicate transfusion management and contribute to a higher rate of postoperative infections.

REFERENCES

1. Bassett AS, McDonald-McGinn DM, Devriendt K, et al: Practical guidelines for managing patients with 22q11.2 deletion syndrome. J Pediatr 159:332-339, e1, 2011
2. McDonald-McGinn DM, Sullivan KE: Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Medicine 90:1-18, 2011
3. McDonald-McGinn DM, Zackai EH: Genetic counseling for the 22q11.2 deletion. Dev Disabil Res Rev 14:69-74, 2008
4. Carotti A, Digilio MC, Piacentini G, et al: Cardiac defects and results of cardiac surgery in 22q11.2 deletion syndrome. Dev Disabil Res Rev 14:35-42, 2008
5. Flashburg MH, Dunbar BS, August G, et al: Anesthesia for surgery in an infant with DiGeorge syndrome. Anesthesiology 58:479-481, 1983
6. Kyburz A, Bauersfeld U, Schinzel A, et al: The fate of children with microdeletion 22q11.2 syndrome and congenital heart defect: clinical course and cardiac outcome. Pediatr Cardiol 29:76-83, 2008
7. Marmon LM, Balsara RK, Chen R, et al: Congenital cardiac anomalies associated with the DiGeorge syndrome: a neonatal experience. Ann Thorac Surg 38:146-150, 1984
8. Schaan BD, Huber J, Leite JC, et al: Cardiac surgery unmasks latent hypoparathyroidism in a child with the 22q11.2 deletion syndrome. J Pediatr Endocrinol Metab 19:943-946, 2006
9. Simsic JM, Coleman K, Maher KO, et al: Do neonates with genetic abnormalities have an increased morbidity and mortality following cardiac surgery? Congenit Heart Dis 4:160-165, 2009
10. Singh VP, Agarwal RC, Sanyal S, et al: Anesthesia for DiGeorge's syndrome. J Cardiothorac Vasc Anesth 11:811, 1997
11. Jacobsen SJ, Xia Z, Campion ME, et al: Potential effect of authorization bias on medical record research. Mayo Clin Proc 74: 330-338, 1999
12. Crifasi PA, Michels VV, Driscoll DJ, et al: DNA fluorescent probes for diagnosis of velocardiofacial and related syndromes. Mayo Clin Proc 70:1148-1153, 1995
13. Manji S, Roberson JR, Wiktor A, et al: Prenatal diagnosis of 22q11.2 deletion when ultrasound examination reveals a heart defect. Genet Med 3:65-66, 2001
14. Cormack RS, Lehane J: Difficult tracheal intubation in obstetrics. Anaesthesia 39:1105-1111, 1984
15. Naqvi N, Davidson SJ, Wong D, et al: Predicting 22q11.2 deletion syndrome: a novel method using the routine full blood count. Int J Cardiol 150:50-53, 2011
16. Deerojanawong J, Chang AB, Eng PA, et al: Pulmonary diseases in children with severe combined immune deficiency and DiGeorge syndrome. Pediatr Pulmonol 24:324-330, 1997
17. Cuneo BF, Langman CB, Ilbawi MN, et al: Latent hypoparathyroidism in children with conotruncal cardiac defects. Circulation 93:1702-1708, 1996
18. Kao A, Mariani J, McDonald-McGinn DM, et al: Increased prevalence of unprovoked seizures in patients with a 22q11.2 deletion. Am J Med Genet A 129A:29-34, 2004
19. Perez E, Sullivan KE: Chromosome 22q11.2 deletion syndrome (DiGeorge and velocardiofacial syndromes). Curr Opin Pediatr 14: 678-683, 2002
20. Cuneo BF: 22q11.2 deletion syndrome: DiGeorge, velocardiofacial, and conotruncal anomaly face syndromes. Curr Opin Pediatr 13: 465-472, 2001
21. Marom T, Roth Y, Goldfarb A, et al: Head and neck manifestations of 22q11.2 deletion syndromes. Eur Arch Otorhinolaryngol 269:381-387, 2012
22. Heinrich S, Birkholz T, Ihmsen H, et al: Incidence and predictors of difficult laryngoscopy in 11,219 pediatric anesthesia procedures. Paediatr Anaesth 22:729-736, 2012
23. Jawad AF, McDonald-Mcginn DM, Zackai E, et al: Immunologic features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). J Pediatr 139:715-723, 2001
24. Goldmuntz E: DiGeorge syndrome: new insights. Clin Perinatol 32:963-978, ix-x, 2005
25. Elder ME: T-cell immunodeficiencies. Pediatr Clin North Am 47: 1253-1274, 2000
26. Collard HR, Boeck A, Mc Laughlin TM, et al: Possible extrathymic development of nonfunctional T cells in a patient with complete DiGeorge syndrome. Clin Immunol 91:156-162, 1999
27. Castro BA: The immunocompromised pediatric patient and surgery. Best Pract Res Clin Anaesthesiol 22:611-626, 2008
28. Ljungman P: Risk of cytomegalovirus transmission by blood products to immunocompromised patients and means for reduction. Br J Haematol 125:107-116, 2004