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Original Article

A population-based study relevant to seasonal variations in causes of death in children undergoing surgery for congenital cardiac malformations

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Abstract *Aims:* Our objectives were, first, to study seasonal distribution of perioperative deaths within 30 days after surgery, and late death, in children undergoing surgery for congenitally malformed hearts, and second, to study the causes of late death. *Methods:* We analysed a retrospective cohort of 1,753 children with congenital cardiac malformations born and undergoing surgery in the period from 1990 through 2002 with a special focus on the causes of late death. The data was obtained from the registry of congenital cardiac malformations at Rikshospitalet, Oslo, and the Norwegian Medical Birth Registry. The mean follow-up from birth was 8.1 years, with a range from zero to 15.2 years. *Results:* During the period of follow-up, 204 (11.6%) of the children died having undergone previous surgery. Of these 124 (7.1%) died in the perioperative period, and 80 (4.5%) were late deaths. There were 56 late deaths during the 6 coldest months, compared with 24 during the 6 warmest months ($p < 0.01$). There was no significant seasonal variation in perioperative deaths. Respiratory infection was the most common cause of late death, and occurred in 25 children, of whom 24 died during the 6 coldest months. Of the 8 sudden late deaths, 7 occurred during the 6 coldest months. There was no seasonal variation for the other causes of death. *Conclusions:* In children undergoing surgery for congenital cardiac malformations in Norway, there is a seasonal variation in late death, with a higher proportion occurring in the coldest months. Death related to respiratory infections predominantly occurs in the winter season, and is the overall most common cause of late death.

Keywords: Mortality; respiratory infection; respiratory syncytial virus; sudden death; Down's syndrome

During the last decade, several studies have identified a significant decrease in perioperative mortality among children undergoing surgery for congenital cardiac malformations.[1–5] In many surgical centres, data is available only for the first 30 postoperative days, and this data is commonly used to document the quality of the care.[4,6–11] Mortality after the first 30 postoperative days, nonetheless, is still significant,[3,12–14] and is related to other factors than those responsible for early death. Previous studies have focused on the cause of death in adults with congenital cardiac malformations,[15] sudden death,[16] and on cause of death in patients with specific cardiac conditions.[17–21]

The aim of our present study was to investigate the seasonal distribution of early and late death, and the causes of late death, in 1,753 children born in the period from 1990 through 2002 who underwent surgery for congenital cardiac malformations at Rikshospitalet, Oslo, Norway. During this period, this centre served as a tertiary centre for

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three-quarters of all children in Norway with congenital cardiac malformations. Detailed clinical information is presented for children who survived the first 30 days after surgery, but subsequently died.

Material and methods

Design

The study is a population-based, retrospective cohort study based on a registry of congenital cardiac malformations.

Sources of data

The registry of congenital cardiac malformations at the Department of Paediatric Cardiology at Rikshospitalet, Oslo, Norway, was used to identify the children suitable for inclusion in the study. The registry contains data on diagnosis, interventions, surgery, and detailed clinical outcome extracted from hospital journals, autopsy reports, as well as information from other hospitals, out-patient clinics, and local doctors. Identification of patients is based on the unique personal identification number from the National Population Registry, which also provides information on date of death or emigration. These data were merged with data from the Norwegian Medical Birth Registry, which includes data on causes of death in children who died the first year of life.

Population

Surgeons at the Rikshospitalet performed 75% of all the cardiac surgical procedures in children in Norway during the period of study. The birth rate in the source population was approximately 45,000 per year over this period. The population identified for inclusion in the study consists of 1,753 liveborn children undergoing surgery for congenital cardiac malformations at Rikshospitalet between January 1, 1990, and September 1, 2002. Only children who underwent open or closed cardiac surgery related to palliation or anatomical correction of structural cardiac defects were included. Children who only underwent procedures as implantation of pacemakers, pericardial drainage, or extracorporeal membrane oxygenation were excluded, as well as children who were treated only with catheter-based interventions. Children with acquired heart disease, arrhythmias, cardiomyopathy, and positional anomalies were excluded from the study if they did not also undergo surgery for structural congenital cardiac defects. Also excluded were 33 children undergoing surgery abroad, and 108 premature infants who underwent surgical closure of persistently patent arterial ducts before the age of two months. Excluding re-operations within 30 days, a total of 2,246 cardiac operations were performed in the population studied during this period.

Data regarding death and emigration was 99% complete for the population on March 1, 2005. For the children who died in the period between Sept. 1, 2002 and March 1, 2005, data regarding surgery and cause of death was updated and included in the analysis.

Variables

Cardiac malformations. Classification of cardiac malformations was based on results from echocardiographic examinations, cardiac catheterisations, and in some instances from findings at surgery or autopsy. The conditions were coded both according to the classification system developed by Van Mierop[22,23] and the 10th edition of the International Classification of Diseases. Based on previous epidemiologic classifications,[24,25] the cardiac malformations were assigned into the following three groups:

- The functionally univentricular arrangement included children registered with hypoplastic left heart syndrome, functionally univentricular physiology, and tricuspid atresia, in whom Fontan palliation was regarded as the ultimate surgical option.
- The group of severe cardiac defects included children with the following 9 conditions: atrioventricular septal defects, concordant atrioventricular and discordant ventriculo-arterial connections, or transposition, double outlet right ventricle, tetralogy of Fallot, totally anomalous pulmonary venous connection, pulmonary atresia with intact ventricular septum, interrupted aortic arch, common arterial trunk, and Ebstein's malformation.
- The groups of less severe cardiac defects included children with other cardiac defects than those placed in the first two groups.

In addition, each child who died was given a principal diagnosis based on the morphologically and/or hemodynamically most important lesions determined by the consensus of two paediatric cardiologists.

Extra-cardiac anomalies. Significant extra-cardiac congenital malformations and syndromes recorded in the registry of congenital cardiac malformations were included in the analysis. Minor anomalies, such as syndactyly of fingers or toes, isolated vascular anomalies of the skin, congenital pigmented naevuses, and congenital dislocation of the hip are examples of anomalies not entered into the registry.

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In 5 children who died, 3 in the perioperative period and 2 late, extra-cardiac anomalies were recorded in the data on causes of death from Norwegian Medical Birth Registry, but not in the registry of congenital cardiac malformations. These data were included in the analysis.

The children were assigned into three groups based on the presence or absence of extra-cardiac anomalies. In the first group there were children with no extra-cardiac anomalies. Allocated to the second group were children with Down's syndrome, provided that Down's syndrome was the only extra-cardiac anomaly. Patients with extra-cardiac anomalies other than Down's syndrome formed the third group.

Seasons. According to the Norwegian Meteorological Institute, the six coldest months in Norway are November through April. This period was defined as the winter season, and the months May through October as the summer season.

Cause of death. Perioperative death was defined as death within 30 days after cardiac surgery. Late death was defined as death later than 30 days after cardiac surgery. In addition, those children who died before discharge from hospital after cardiac surgery, but more than 30 days after the operation, were included as late deaths. Based on the available data, the cause of late deaths was determined by the consensus of two paediatric cardiologists (Eskedal and Thaulow). In children who died outside hospital without having an autopsy performed, information from primary health care centres and local doctors was used to determine the cause of death. Six categories of late death were defined:

- The group with respiratory infection included children diagnosed with infections in the upper or lower respiratory tract.
- The group with non-respiratory infection included children with the diagnoses of septicaemia, gastroenteritis, and unspecified viral infection (International Classification of Diseases, 9th edition: 079.9).

Children in these first two categories included those who died in hospital who were diagnosed with infection during the final hospital admission, those with diagnosed infection at autopsy, and those with infection diagnosed outside hospital the during the last 7 days of life.

- The category of sudden death included children with unexpected instantaneous death, or death within 24 hours after the onset of acute symptoms or signs (International Classification of Diseases, 9th edition: 798, International Classification of Diseases, 10th edition: R96).
- The group of procedure related deaths included children who died as a consequence of cardiac catheterisation or non-cardiac surgical procedures.
- The group of those with other non-cardiac deaths included children with trisomy 13, Werdnig-Hoffman disease, and children who died from an external cause of injury or from malignant disease.
- The final group of cardiovascular death included all those children not allocated to one of the other five categories, which also contained children who died due to progressive myocardial failure or nonsudden death secondary to arrhythmia.

Statistical analyses. Frequencies and percentages were used to summarize the data. Cross tabulation with p values from Pearson x^2 tests plus odds ratios as a measure of effect size were used. Version 13.0 of the Statistical Product and Service Solutions was used in the calculations. A p value less than 0.05 was considered statistically significant.

Ethical considerations. The study was approved by the Regional Committee for Medical Research, the Norwegian Data Inspectorate, and the Norwegian Directorate of Health and Social Services.

Results

Of the children included, 141 (8%) had a functionally univentricular arrangement, 641 (36.6%) had severe cardiac defects and 971 (55.4%) had less severe cardiac defects. Down's syndrome was registered in 209 children (11.9%), and extra-cardiac anomalies other than Down's syndrome in 197 (11.2%). Of the children with Downs's syndrome, 9 had additional extra-cardiac anomalies. Of the 1,753 children undergoing surgery, 204 (11.6%) died during follow-up, with 124 (7.1%) dying in the perioperative period, and 80 (4.5%) late deaths. Age at initial cardiac surgery was less than 1 month in 29% of the children, and less than 12 months in 70%. Mean follow-up from birth was 8.1 years, with a range from zero to 15.2 years.

Of the children with the functionally univentricular arrangement, 36 (26%) died in the perioperative period, and 14 (10%) died subsequently. Of children with severe cardiac defects, 60 (9%) died in the perioperative period, and 39 (6%) subsequently. In children with less severe cardiac defects, there were 28 perioperative (3%) deaths, and 27 (3%) late deaths. Death in the perioperative period occurred in 10 (5%) children with Down's syndrome, and late deaths in 14 (7%) children. Children with extra-cardiac anomalies other than

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Down's syndrome suffered 17 (7%) perioperative deaths, and 20 (10%) late deaths. Gender was evenly distributed in children who died in the perioperative period, with 63 males and 61 females.

Seasonal distribution of deaths

Of the total number of cardiac operations, excluding reoperations performed within 30 days, 1,097 (48.8%) were performed during the winter season. The month of birth was evenly distributed in the cohort, with 882 (50.4%) born in winter season.

In Figure 1, we show perioperative and late deaths occurring during the winter and summer season. There was no significant difference in seasonal distribution of perioperative deaths. There were, however, significantly more late deaths during the winter season ($p < 0.001$). Excluding perioperative deaths, the children remaining at risk of late death were equally distributed regarding season of birth, with 815 (50%) born in winter season.

Causes of late death

Cause of death could be determined in 78 of the 80 children dying late. Autopsy was performed in 41 children with late deaths, with 9 children dying outside hospital not submitted to autopsy.

In Figure 2, we show the seasonal distribution of the causes of death in the 78 children dying late. The cause of death was more likely to be a respiratory infection if death occurred during winter season compared with death occurring during summer season, with an odds ratio of 17.3, and 95% confidence intervals from 2.2 to 137, giving a p value of less than 0.01. The odds ratio for the cause of death to be an infection, be it respiratory or non-respiratory, was 3.3 for children who died in the winter season compared with children who died in the summer season, with 95% confidence intervals from 1.2 to 9.0, and p equal to 0.02.

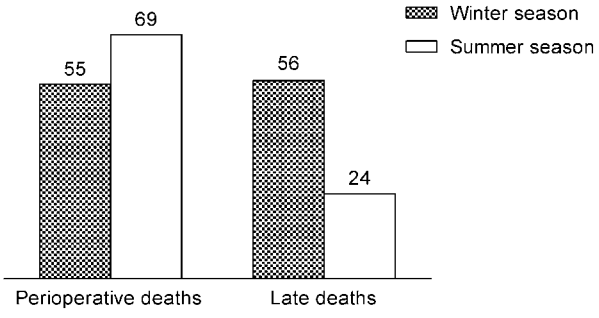

Figure 1.
Seasonal distribution of perioperative deaths and late deaths in children undergoing surgery for congenital cardiac malformations.

There were 7 children who died suddenly in the winter, and only one in the summer season. Autopsy was performed in only 2 of these 8 children. Of 8 sudden deaths registered, 4 occurred before the age of one year. In 3 of the 8, there was a functional univentricular arrangement palliated with a central shunt, 2 had double outlet right ventricle, 1 had an atrioventricular septal defect, 1 had Ebstein's malformation, and 1 one had an atrial septal defect in the setting of Down's syndrome. Of the children who died suddenly in the winter season, 3 were recovering after a respiratory infection.

The 20 cardiovascular deaths were evenly distributed in regard to season. There were 4 children who died before discharge from hospital, 14 died in hospital after re-admission, and 2 died outside hospital, with 3 children with Down's syndrome, and 4 having extra-cardiac anomalies other than Down's syndrome. Persistent pulmonary hypertension was registered in 5 children, and arrhythmias in 4 children. There were 4 children with a functionally univentricular arrangement, 7 had severe cardiac defects, and 9 had less severe cardiac defects. The principal cardiac diagnoses for the 9 children with less severe cardiac defects were coarctation of the aorta and ventricular septal defect in 3, coarctation of the aorta in 2, congenitally corrected transposition, tetralogy of Fallot with

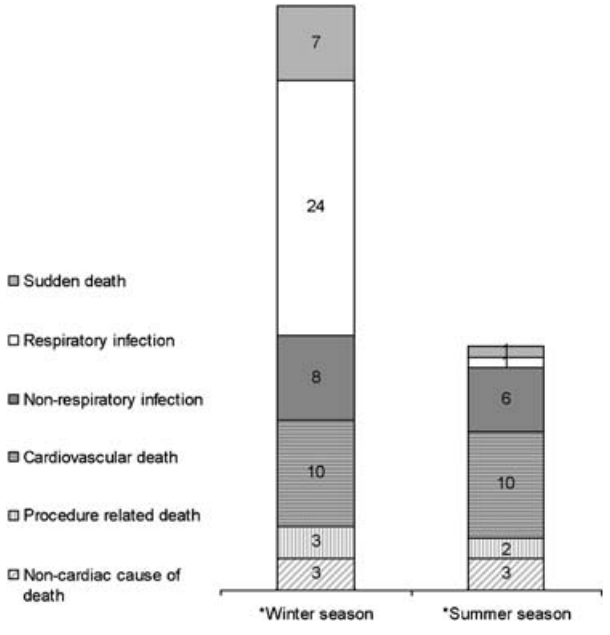

Figure 2.
*Seasonal distribution of causes of late death in children undergoing surgery for congenital cardiac malformations. * Cause of death unknown in one child who died in winter season and in one child who died in summer season.*

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pulmonary atresia, valvar aortic stenosis, and ventricular septal defect.

The 5 procedurally related deaths included 2 children who died during cardiac catheterisation, and 3 who died during non-cardiac surgical procedures. The 6 non-cardiac causes of death were due to trisomy 13 in 2, Werdnig Hoffmann disease, multiple non-cardiac anomalies, external accident, and one death due to malignancy. The principal cardiac diagnosis in the children who died from non-cardiac causes were atrial septal defect in 2, ventricular septal defect in 2, and one each with tetralogy of Fallot with pulmonary stenosis and with pulmonary atresia.

In Table 1, we list the clinical diagnoses and aetiological agents in children who died with an infection. Among 25 children who died of a respiratory infection, only one died during the summer season, this being diagnosed as an unspecified respiratory infection.

There were 5 children who died in hospital subsequent to infection by the respiratory syncytial virus. All died before the age of two years, with 4 of the 5 dying before they were one year old. Of these, 3 had a severe cardiac defect, and one had a functionally univentricular arrangement. Another child had pulmonary hypertension, and 3 were cyanotic before acquiring the viral infection. None had received prophylaxis with palivizumab.

In the 14 children who died with a non-respiratory infection, 6 died in the summer season, 5 with a clinical diagnosis of septicaemia, and one with unspecified viral infection.

None of the children who died with an infection were coded with influenzal infection according to International Classification of Diseases, 9th or 10th edition.

In Table 2, we show the distribution of cardiac defects and associated non-cardiac anomalies in all children dying late, and in the children who died with a respiratory or non-respiratory infection. In children who died from a respiratory infection, one-third had Down's syndrome. We compared the 10 children with Down's syndrome who either died in the perioperative period, the 14 dying late, and the 185 who survived, finding no differences in distribution of gender, gestational age, birth weight or age at initial cardiac surgery.

In Table 3, we show gender, survival-time after last cardiac surgery, age at time of death and place of death for all children dying late, and for children who died with an associated infection. Gender and survival-time after last cardiac surgery were evenly distributed in the 3 categories of late death. The majority of all late deaths occurred before the children were two years old, and 44 (55%) children died before the age of one year. The group with respiratory infections had the highest proportion of deaths during the first two years of life, with 80% of deaths occurring before the age of 2 years. Survival after the last cardiac surgery was short, with a median survival in the range from 4 to 6 months in all 3 groups.

Table 1. Clinical diagnosis and etiologic agent in children who died related to infections.

Clinical diagnosis		Etiologic agent	
	n		*n*
Respiratory infection ($n = 25$)			
Pneumonia	6	Respiratory syncytial virus[1]	1
		Klebsiella pneumoniae[2]	1
Bronchopneumonia	5	*Staphylococcus aureus* and *Acinetobacter sp*[2]	1
		Streptococcus pneumoniae[2]	1
Bronchiolitis	5	Respiratory syncytial virus[1]	4
Pharyngitis	2		
Tonsilitis	1		
Unspecified respiratory infection	6	*Streptococcus pneumoniae*[3]	1
Non-respiratory infection ($n = 14$)			
Septicaemia	11	*Streptococcus pneumoniae*[3]	1
		Gram positive coccus[3]	1
		Coagulase negative staphylococcus[3]	2
		Coagulase negative staphylococcus and Gram positive coccus[3]	1
Gastroenteritis	2	Rotavirus[4]	1
Unspecified viral infection	1		

[1]: Respiratory syncytial virus detected in nasopharyngeal secretions.
[2]: Isolated from lungs at autopsy.
[3]: Isolated in blood culture.
[4]: Detected in faeces.

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Table 2. Cardiac malformations and associated extra-cardiac anomalies in all late deaths and in children who died related to infections.

	All late deaths ($n = 80$)		**Respiratory infection ($n = 25$)**		**Non-respiratory infection ($n = 14$)**	
	n **(%)**		***n***		***n***	
Cardiac defect						
Functionally univentricular arrangement	14 (18%)		2		5	
Double inlet ventricle or AV atresia		11		1		4
Hypoplastic left heart syndrome		3		1		1
Severe cardiac defects	39 (49%)		17		7	
Atrioventricular septal defect		14		9		2
Tetralogy of Fallot		7		3		1
Double outlet right ventricle		5		2		
Transposition		4		1		1
Pulmonary atresia with intact ventricular septum		3		1		
Common arterial trunk		3		1		2
Ebstein's malformation		2				
Interrupted Aortic arch		1				1
Less severe cardiac defects	27 (34%)		6		2	
Ventricular septal defect		6		3		
Tetralogy with pulmonary atresia		4		1		1
Coarction of the aorta and VSD		3				
Coarction of the aorta		3		1		
Aortic stenosis		3				1
Congenitally corrected transposition		3				
Atrial septal defect		3				
Anomaly of Coronary Artery		1		1		
Double Aortic arch		1				
Associated non-cardiac anomalies						
No associated anomalies	46 (58%)		12		7	
Down's syndrome	14 (18%)		8		2	
Associated anomaly other than Down's	20 (25%)		5		5	
Asplenia		4				2
Multiple malformations, unclassified		3		1		
Gastrointestinal malformation		3				1
Trisomy 13		2				
VACTERL syndrome		1		1		
DiGeorge syndrome		1				1
Malformation of central nervous system		1				1
Cleft lip/palate		1		1		
Werdnig-Hoffmann disease		1				
Apert's syndrome		1				
Noonan syndrome		1		1		
Rubinstein-Taby syndrome		1		1		

AV = atrioventricular, VSD = ventricular septal defect.

Table 3. Gender, survival time after surgery, age and place of death in all late deaths and in children who died related to infections.

	All late deaths ($n = 80$)	**Respiratory infection ($n = 25$)**	**Non-respiratory infection ($n = 14$)**
Gender (male/female)	41/39	12/13	9/5
Survival time after last cardiac surgery (months; median, (range))	5.8 (1.1–120)	4.8 (1.5–106)	4.5 (1.1–39)
Age at death (months; median, (range))	10.8 (1.6–142)	8.8 (2.6–125)	12.1 (1.6–53)
Age $<$ 2 years (n, (%))	58 (73%)	20	10
Death in hospital, before discharge after surgery (n, (%))	11 (14%)	0	3
Death in hospital, re-admission (n, (%))	49 (61%)	20	9
Death during transportation or within 1 hour after arrival at emergency department (n, (%))	5 (6%)	1	1
Death outside hospital (n, (%))	15 (19%)	4	1

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Late deaths before discharge from hospital after cardiac surgery

There were 11 children who died in the range of 34 to 90 days after the last operation, and 9 of them died before 1 year of age, with 6 dying in the winter season. The causes of death in these 11 children were septicaemia in 2, gastroenteritis in 1, death during cardiac catheterisation for 2, sudden death in 1, Werdnig Hoffmann disease in 1, and the final 4 deaths due to progressive cardiac failure. Associated non-cardiac anomalies were found in 5 of the 11 children, with 2 having Down's syndrome. The cardiac diagnosis was a functionally univentricular arrangement in 3, atrioventricular septal defect in 3, aortic stenosis in 2, coarctation of the aorta in 2, and ventricular septal defect in the final child.

Discussion

In this study, we present data on the deaths of children undergoing surgery for cardiac malformations as based on follow-up information we hold on children born in Norway between 1990 to 2002. Late deaths after surgery accounted for two-fifths of all deaths occurring in our cohort of patients. We found that such late death was more than two times more likely to occur during the winter season than in the summer season. Excluding perioperative deaths, the children left at risk of late death showed no seasonal variation in season of birth or season of cardiac surgery that could influence the seasonal distribution of late deaths. Of the 11 children who died before discharge from hospital, but later than 30 days after surgery, 6 died during the winter season. Reclassification of these children to the group of those dying in the perioperative period had no impact on our conclusions.

There was a clear seasonal difference in causes of late death, especially respiratory infections, which were significantly more common as a cause of death during the winter period. It is difficult to be completely sure, in retrospect, about the leading cause of death. We found a striking seasonal difference, nonetheless, in the occurrence of late deaths, and this finding seems to be associated with the higher proportion of deaths caused by respiratory infections deaths during the winter season. Our data does not contain detailed information of how many children who survived respiratory infections throughout the year, and the risk of death due to a respiratory infection cannot be estimated. We also have to take account that the climate in Norway, with low temperatures in the winter months, might be a risk factor of death in itself in children with limited cardiac reserves. If so, the impact of season on mortality would be greater in countries with cold winters as compared with countries with mild climate throughout the year.

The impact of respiratory infection has been described both in adults[26,27] and children with cardiac disease.[28,29] In agreement with the present results, it has been documented in studies from national health registries that infection with both the influenza and respiratory syncytial viruses are major contributors to deaths and morbidity in children in general.[30–32] It is also known that children with cardiac malformations are at particular risk of serious infection by the respiratory syncytial virus.[29,32–34] In our study, only 5 of the 25 children who died from a respiratory infection had a verified infection with the respiratory syncytial virus. Since our data is obtained retrospectively, this number is probably too low, especially when taking account of the high prevalence of infection by the respiratory syncytial virus in hospitalised children under the age of one year in general.[32] There are several recent publications on the safety, efficacy and economic implication of prophylaxis with palivizumab in children with cardiac malformations.[35–40] Palivizumab has been used for prophylaxis in a few children with cardiac malformations in Norway since 1999, but our period of study is mainly from the time before palivizumab was introduced. Immunisation with palivizumab has, in one trial, been shown to be effective in reducing hospitalisation caused by respiratory syncytial virus in children with cardiac malformations, but mortality was not significantly reduced.[40] Also important is that this trial enrolled only children with unoperated or partially corrected cardiac defects in a stable condition, and with no associated non-cardiac anomalies. We observe that in our cohort of children undergoing cardiac surgery, more than half of the children who died with an associated respiratory infection after the immediate postoperative period had associated non-cardiac anomalies.

It proved possible to isolate *Streptococcus pneumonia* in 3 children who died. In Norway, vaccination against pneumococcal disease was not routinely performed during the period of study unless there was also an accompanying immune defect. Our study did not identify any late deaths with a terminal infection due to influenza virus. This might be because of the limitations of our retrospective data.

Sudden death occurred in 8 of the 1,629 children who survived the first 30 days after cardiac surgery. This is lower than previously reported,[16,41] and may relate to the relatively short follow-up time in our study. An increased incidence of sudden death during the winter season has been reported in the

general population,[42–44] which is in agreement with the present observations. It may be that sub-clinical infections are of importance for sudden death in patients with a low cardiovascular reserve, but our data cannot answer this suggestion.

The complexity of the cardiac malformations was higher in the group of children dying late, with two thirds having either severe cardiac defects or a functionally univentricular arrangement, as compared with 45% in the total population studied. Furthermore, there was a high prevalence of associated extra-cardiac anomalies, these being found in 43% of children dying late, compared to 23% in the total population. This contrasts with the observations in children who died in the perioperative period, where associated extra-cardiac anomalies were registered in only 22%. The available data on extra-cardiac anomalies was more extensive in children who died than in children who survived in our study. If excluding extra-cardiac anomalies exclusively reported in the Norwegian Medical Birth Registry, the prevalence of extra-cardiac anomalies in late deaths would still be 40%. Given the limitations of analysing data culled from a register, the definite prevalence of extra-cardiac anomalies is probably higher than we report.

We have previously shown that overall survival improved in children with congenital cardiac anomalies born from 1995 to 1999, as compared to children born from 1990 to 1995, but this did not include children with extra-cardiac anomalies other than Down's syndrome.[45] The group of children with cardiac malformations and associated extra-cardiac anomalies other than Down's syndrome accounts for one-quarter of late deaths, in contrast to just over one-tenth in the total population, and one-sixth of the perioperative deaths. Down's syndrome was registered more often in those dying late, specifically in just under one-fifth, compared with just over one-tenth of the total population. Down's syndrome was present in onethird of the children dying late from respiratory infections. This observation is in agreement with previous reports, which have shown that respiratory infections are leading causes of death in children with cardiac malformations and Down's syndrome.[46,47]

Our population is made up of children born in a decade in which paediatric cardiac surgery has made great advances in improving perioperative survival, despite the fact that more children with complex cardiac defects are undergoing surgery at an ever younger age.[1,3] In our study, the majority of children dying late were aged less than 2 years, and over half of these children died before they reached the age of one year. Survival after the last cardiac operation was short, with a median time under 6 months.

In most studies, the judgement of the quality of care is based on observations obtained during the first 30 days after surgery.[4,6–11] Our study extends this data, and suggests that children undergoing surgery for complex cardiac malformations represent a group at high risk during the first two years of life, particularly when additional extra-cardiac anomalies are present. Programmes for immunisation, close follow-up after cardiac surgery, and early hospitalisation when symptoms are detected of respiratory infections, might reduce late mortality. Our retrospective data, nonetheless, does not allow definite conclusions. Only prospective studies can provide clear evidence of which measures will be effective.

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References

1. Grech V, Elliott MJ. Evolution of surgical trends in congenital heart disease: a population based study. Int J Cardiol 1998; 66: 285–292.
2. Lundstrom NR, Berggren H, Bjorkhem G, Jogi P, Sunnegardh J. Centralization of pediatric heart surgery in Sweden. Pediatr Cardiol 2000; 21: 353–357.
3. Eskedal L, Hagemo PS, Eskild A, Aamodt G, Seiler KS, Thaulow E. Survival after surgery for congenital heart defects: does reduced early mortality predict improved long-term survival? Acta Paediatr 2005; 94: 438–443.
4. Stark J, Gallivan S, Lovegrove J, et al. Mortality rates after surgery for congenital heart defects in children and surgeons' performance. Lancet 2000; 355: 1004–1007.
5. Frid C, Bjorkhem G, Jonzon A, Sunnegardh J, Anneren G, Lundell B. Long-term survival in children with atrioventricular septal defect and common atrioventricular valvar orifice in Sweden. Cardiol Young 2004; 14: 24–31.
6. Moller JH, Powell CB, Joransen JA, Borbas C. The pediatric cardiac care consortium–revisited. Jt Comm J Qual.Improv 1994; 20: 661–668.
7. Jenkins KJ, Gauvreau K. Center-specific differences in mortality: preliminary analyses using the Risk Adjustment in Congenital Heart Surgery (RACHS-1) method. J Thorac Cardiovasc Surg 2002; 124: 97–104.
8. Lacour-Gayet F, Clarke DR. The Aristotle method: a new concept to evaluate quality of care based on complexity. Curr Opin Pediatr 2005; 17: 412–417.
9. Lacour-Gayet F, Clarke D, Jacobs J, et al. The Aristotle score for congenital heart surgery. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2004; 7: 185–191.

10. Lacour-Gayet F, Clarke D, Jacobs J, et al. The Aristotle score: a complexity-adjusted method to evaluate surgical results. Eur J Cardiothorac Surg 2004; 25: 911–924.
11. Stark JF, Gallivan S, Davis K, et al. Assessment of mortality rates for congenital heart defects and surgeons' performance. Ann Thorac Surg 2001; 72: 169–174.
12. Gibbs JL, Monro JL, Cunningham D, Rickards A. Survival after surgery or therapeutic catheterisation for congenital heart disease in children in the United Kingdom: analysis of the central cardiac audit database for 2000-1. BMJ 2004; 328: 611.
13. Nieminen HP, Jokinen EV, Sairanen HI. Late results of pediatric cardiac surgery in Finland: a population-based study with 96% follow-up. Circulation 2001; 104: 570–575.
14. Morris CD, Menashe VD. 25-year mortality after surgical repair of congenital heart defect in childhood. A population-based cohort study. JAMA 1991; 266: 3447–3452.
15. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. Am J Cardiol 2000; 86: 1111–1116.
16. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol 1998; 32: 245–251.
17. Nollert G, Fischlein T, Bouterwek S, Bohmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. J Am Coll Cardiol 1997; 30: 1374–1383.
18. Fenton KN, Siewers RD, Rebovich B, Pigula FA. Interim mortality in infants with systemic-to-pulmonary artery shunts. Ann Thorac Surg 2003; 76: 152–156.
19. Keane JF, Driscoll DJ, Gersony WM, et al. Second natural history study of congenital heart defects. Results of treatment of patients with aortic valvar stenosis. Circulation 1993; 87: I16–I27.
20. Young D, Mark H. Fate of the patient with the Eisenmenger syndrome. Am J Cardiol 1971; 28: 658–669.
21. Kopf GS, Mello DM. Surgery for congenital heart disease in low-birth weight neonates: a comprehensive statewide Connecticut program to improve outcomes. Conn Med 2003; 67: 327–332.
22. Van Mierop LH. Diagnostic code for congenital heart disease. Pediatr Cardiol 1984; 5: 331–362.
23. Van Mierop LH. Diagnostic code for congenital heart disease, supplement. Pediatr Cardiol 1986; 7: 31–34.
24. Pradat P, Francannet C, Harris JA, Robert E. The epidemiology of cardiovascular defects, part I: a study based on data from three large registries of congenital malformations. Pediatr Cardiol 2003; 24: 195–221.
25. Harris JA, Francannet C, Pradat P, Robert E. The epidemiology of cardiovascular defects, part 2: a study based on data from three large registries of congenital malformations. Pediatr Cardiol 2003; 24: 222–235.
26. Fleming DM, Cross KW, Pannell RS. Influenza and its relationship to circulatory disorders. Epidemiol Infect 2005; 133: 255–262.
27. Meyers DG. Could influenza vaccination prevent myocardial infarction, stroke and sudden cardiac death? Am J Cardiovasc Drugs 2003; 3: 241–244.
28. Moler FW, Khan AS, Meliones JN, Custer JR, Palmisano J, Shope TC. Respiratory syncytial virus morbidity and mortality estimates in congenital heart disease patients: a recent experience. Crit Care Med 1992; 20: 1406–1413.
29. MacDonald NE, Hall CB, Suffin SC, Alexson C, Harris PJ, Manning JA. Respiratory syncytial viral infection in infants with congenital heart disease. N Engl J Med 1982; 307: 397–400.
30. Fleming DM, Pannell RS, Cross KW. Mortality in children from influenza and respiratory syncytial virus. J Epidemiol Community Health 2005; 59: 586–590.
31. Anderson LJ, Parker RA, Strikas RL. Association between respiratory syncytial virus outbreaks and lower respiratory tract deaths of infants and young children. J Infect Dis 1990; 161: 640–646.
32. Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. J Pediatr 2003; 143: S127–S132.
33. Bonnet D, Schmaltz AA, Feltes TF. Infection by the respiratory syncytial virus in infants and young children at high risk. Cardiol Young 2005; 15: 256–265.
34. Cabalka AK. Physiologic risk factors for respiratory viral infections and immunoprophylaxis for respiratory syncytial virus in young children with congenital heart disease. Pediatr Infect Dis J 2004; 23: S41–S45.
35. Saji T, Nakazawa M, Harada K. Safety and efficacy of palivizumab prophylaxis in children with congenital heart disease. Pediatr Int 2005; 47: 397–403.
36. Tulloh RM, Feltes TF. The European Forum for Clinical Management: prophylaxis against the respiratory syncytial virus in infants and young children with congenital cardiac disease. Cardiol Young 2005; 15: 274–278.
37. Rackham OJ, Thorburn K, Kerr SJ. The potential impact of prophylaxis against bronchiolitis due to the respiratory syncytial virus in children with congenital cardiac malformations. Cardiol Young 2005; 15: 251–255.
38. Wegner S, Vann JJ, Liu G, et al. Direct cost analyses of palivizumab treatment in a cohort of at-risk children: evidence from the North Carolina Medicaid Program. Pediatrics 2004; 114: 1612–1619.
39. Yount LE, Mahle WT. Economic analysis of palivizumab in infants with congenital heart disease. Pediatrics 2004; 114: 1606–1611.
40. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003; 143: 532–540.
41. Pelech AN, Neish SR. Sudden death in congenital heart disease. Pediatr Clin North Am 2004; 51: 1257–1271.
42. Straus SM, Bleumink GS, Dieleman JP, van der LJ, Stricker BH, Sturkenboom MC. The incidence of sudden cardiac death in the general population. J Clin Epidemiol 2004; 57: 98–102.
43. Messner T, Lundberg V. Trends in sudden cardiac death in the northern Sweden MONICA area 1985-99. J Intern Med 2003; 253: 320–328.
44. Arntz HR, Willich SN, Schreiber C, Bruggemann T, Stern R, Schultheiss HP. Diurnal, weekly and seasonal variation of sudden death. Population-based analysis of 24,061 consecutive cases. Eur Heart J 2000; 21: 315–320.
45. Eskedal L, Hagemo P, Eskild A, Aamodt G, Seiler KS, Thaulow E. A population-based study of extra-cardiac anomalies in children with congenital cardiac malformations. Cardiol Young 2004; 14: 600–607.
46. Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. Lancet 2002; 359: 1019–1025.
47. Mikkelsen M, Poulsen H, Nielsen KG. Incidence, survival, and mortality in Down syndrome in Denmark. Am J Med Genet Suppl 1990; 7: 75–78.