Optimizing the delivery and use of a new monoclonal antibody in children with congenital heart disease: A successful provincial respiratory syncytial virus prophylaxis program

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OBJECTIVES: To describe a program for passive immunization against respiratory syncytial virus infection in infants with hemodynamically significant congenital heart disease (CHD) in accordance with the Canadian Paediatric Society recommendations.

METHODS: A provincial coordinating committee composed of specialists in pediatrics, cardiology, infectious diseases, neonatology and public health collaborated to develop and implement a program to identify children with hemodynamically significant heart disease and offer respiratory syncytial virus prophylaxis. Database records for all children younger than two years of age who were seen by the provincial pediatric cardiology referral service were reviewed. Children with hemodynamically significant heart disease, as determined by a clinical assessment and echocardiography, were considered to be eligible for monthly palivizumab prophylaxis for five winter months. All physicians in the province were notified that approval of the provincial cardiology service was required for prophylaxis to be administered. Immunization rates were compared with projected rates based on the expected population-based immunization rates in infants with CHD in other provinces.

RESULTS: 401 children with any cardiac diagnoses were identified, representing 545 potential patient-seasons of prophylaxis over two years in a birth cohort of 20,173 and 19,227 children, in each respective season (13.8 patient-seasons per 1000 births). Of these, 21 children were eligible for palivizumab prophylaxis according to the Canadian Paediatric Society criteria. All eligible children were immunized, and no ineligible children received the immunization. A review of palivizumab use in other provinces revealed highly variable rates of prophylaxis.

CONCLUSIONS: The use of palivizumab for children with CHD can be optimized through a provincial model, in which children requiring prophylaxis are prospectively identified and reviewed by pediatric cardiologists – and to whom evidence-based guidelines developed by a multidisciplinary team – are applied. Such a model ensures that all patients requiring prophylaxis receive the appropriate immunization and avoids the immunization of low-risk children with CHD, in whom the benefits of palivizumab have not been proven.

Key Words: Congenital heart disease; Palivizumab; Respiratory syncytial virus

L'optimisation de la délivrance et de l'utilisation d'un nouvel anticorps monoclonal chez des enfants atteints d'une cardiopathie congénitale : Un programme provincial efficace de prophylaxie contre le virus respiratoire syncytial

OBJECTIFS : Décrire un programme d'immunisation passive contre l'infection par le virus respiratoire syncytial chez des nourrissons atteints d'une cardiopathie congénitale importante sur le plan hémodynamique, conformément aux recommandations de la Société canadienne de pédiatrie.

MÉTHODOLOGIE : Un comité de coordination provincial composé de spécialistes de la pédiatrie, de la cardiologie, de l'infectiologie, de la néonatalogie et de la santé publique a collaboré à l'élaboration et à l'implantation d'un programme visant à repérer les enfants atteints d'une cardiopathie importante sur le plan hémodynamique et à leur offrir une prophylaxie contre le virus respiratoire syncytial. On a analysé les dossiers informatisés de tous les tout-petits de moins de deux ans qui étaient passés par le service provincial de consultation en cardiologie pédiatrique. Les enfants atteints d'une cardiopathie importante sur le plan hémodynamique, déterminée par une évaluation clinique et une échocardiographie, étaient jugés admissibles au programme mensuel de prophylaxie au palivizumab pour les cinq mois de l'hiver. On a avisé tous les médecins de la province qu'ils devaient obtenir l'approbation du service provincial de cardiologie avant d'administrer la prophylaxie. On a comparé les taux d'immunisation à ceux projetés d'après les taux d'immunisation prévus en population chez les enfants des autres provinces atteints d'une cardiopathie congénitale.

RÉSULTATS : On a repéré 401 enfants atteints d'une cardiopathie diagnostiquée, représentant 545 saisons-patient potentielles de prophylaxie sur deux ans, au sein d'une cohorte de naissances de 20 173 et 19 227 enfants au cours de chacune de ces saisons, respectivement (13,8 saisons-patient pour 1 000 naissances). De ce nombre, 21 enfants étaient admissibles à la prophylaxie au palivizumab d'après les critères de la Société canadienne de pédiatrie. Tous les enfants admissibles ont été vaccinés, tandis qu'aucun enfant non admissible ne l'a été. Une analyse du recours au palivizumab dans les autres provinces a révélé une très grande variabilité de l'immunisation.

CONCLUSIONS : Il est possible d'optimiser l'utilisation du palivizumab chez les enfants atteints d'une cardiopathie congénitale à l'aide d'un modèle provincial selon lequel les enfants ayant besoin d'une prophylaxie sont repérés de manière prospective et évalués par des cardiologues pédiatriques, et à qui on applique des lignes directrices probantes élaborées par une équipe multidisciplinaire. Un tel modèle garantit que tous les patients qui ont besoin d'une prophylaxie reçoivent les vaccins pertinents, tout en évitant la vaccination des enfants atteints d'une cardiopathie congénitale qui sont peu vulnérables, car les bienfaits du palivizumab ne sont pas démontrés dans leur cas.

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Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection in early childhood and leads to hospitalization in up to 2% of Canadian children younger than two years of age each winter (1). Children with hemodynamically significant cardiac disease may develop respiratory or cardiac failure during RSV infection, and have prolonged hospital stay, need intensive care and have higher mortality rates than healthy infants (2); they may also have worse postoperative clinical outcomes after corrective cardiac surgery (3,4). Seasonal prophylaxis with a humanized mouse monoclonal anti-RSV antibody (palivizumab, Abbott Laboratories, Canada) (5), reduces RSV-related hospitalization rates in children with hemodynamically significant heart disease, and Canadian authorities recommended in 2003 that eligible children be considered for passive immunization during the winter (6,7).

The cost of palivizumab is substantial, with one season of prophylaxis (five doses) costing approximately \$7,500 in drug costs alone. In the setting of limited health care resources, it is important that only those who are truly at risk receive this intervention. The eligibility criterion of 'hemodynamically significant' heart disease is open to clinical interpretation. In the efficacy trial that led to approval of palivizumab for children with congenital heart disease (CHD) (5), pediatric cardiologists determined whether heart disease was hemodynamically significant, and children with uncomplicated defects were excluded. However, in most Canadian jurisdictions, any physician can now order palivizumab. Some Canadian jurisdictions have noted a surge in palivizumab use since the publication of the palivizumab trial and following the release of the Canadian Paediatric Society recommendations (8).

We describe a provincial program developed to avoid the inappropriate prescribing of palivizumab to low-risk infants with heart disease while ensuring coverage for eligible children with CHD at increased risk of RSV-associated hospitalization. We also sought to estimate rates of children with CHD who were given palivizumab in other provinces.

METHODS

Program

The IWK Health Centre (IWK) is a university-affiliated, 180-bed, pediatric, women's and maternity care institution in Halifax, Nova Scotia, and serves as the tertiary care pediatric referral centre for the Maritime provinces (population of approximately two million). As the only children's hospital in Nova Scotia, it houses the only pediatric cardiology service, and all children with CHD in Nova Scotia are followed through the Children's Heart Centre in Halifax. Information on all these children is prospectively entered into a pediatric cardiology database maintained by the Division of Pediatric Cardiology at the IWK.

The Nova Scotia Provincial Blood Coordinating Program (NSPBCP), under the authority of the provincial Ministry of Health, convened a provincial committee with physicians, nurses and administrators representing pediatric cardiology, infectious diseases, neonatology and community pediatrics, as well as general practitioners, and representatives from provincial public health departments, to assist in developing overall guidelines for palivizumab use. The cardiology program described in the present paper is separate from, but nested within, the global palivizumab program. Under the guidelines developed, physicians wishing to provide palivizumab for their patients must complete a form

indicating which eligibility criteria are fulfilled and forward it to the NSPBCP before a product is released.

In the fall of 2003, patients younger than two years of age were identified through a search of the IWK cardiology database by a cardiologist and a cardiac clinic nurse. Files of all children with potentially serious forms of CHD were reviewed to determine eligibility for RSV prophylaxis based on clinical criteria, including echocardiography. The Canadian Paediatric Society guidelines (6) for the administration of palivizumab have indicated that it should be given to children with 'hemodynamically significant' cardiac disease. For the purposes of this program, children with hemodynamically significant cyanotic or acyanotic CHD were defined as those requiring corrective surgery or those who were on cardiac medication for hemodynamic considerations (6). Children with uncomplicated defects or complicated lesions adequately corrected by surgery and not requiring medications for congestive heart failure without other risk factors were not eligible. A list with approved patient identifiers was sent to the NSPBCP, so that when requests were received, they could be dispensed promptly.

If requests were received for cardiac patients who were not on the preapproved list, the NSPBCP requested an opinion from the Children's Heart Centre on the appropriateness of immunization. If children with CHD were born during the RSV season, their names were forwarded to the NSPBCP. The patient's parents or guardians and their physicians were contacted to alert them to the recommendation for palivizumab prophylaxis, and the primary care physician ordered the product. Children living in Halifax visited a RSV prevention clinic at the IWK, which provides monthly immunization throughout the winter months for eligible children, along with education on prevention of respiratory infections. Outside Halifax, the local physician was responsible for palivizumab administration.

Once a child had begun a course of prophylaxis, the course was normally carried to completion, regardless of whether the child's age changed during the study period. Children were not routinely reimmunized after cardiopulmonary bypass to boost immunoglobulin G levels. Immunization was not continued after surgical repair of a heart lesion if there was no residual hemodynamic defect. The RSV season was determined through laboratory surveillance at the IWK and continued for five months from season opening.

Estimates of product use

Palivizumab use data for Nova Scotia were obtained from the NSPBCP and for British Columbia were obtained through British Columbia's Provincial Blood Coordinating Office. Data for other provinces were collected by Abbott Laboratories Ltd, and provided for the present paper courtesy of Canadian Blood Services after permission was obtained from individual provincial and territorial blood representatives. Data for the province of Quebec were obtained from a published source for the 2003/2004 season (8).

Estimates of expected and actual prophylaxis rates in other provinces

Children with hemodynamically significant CHD were potentially eligible for RSV prophylaxis if they were younger than two years of age at the start of the RSV prophylaxis season. For the purposes of calculation, the RSV season was assumed to run from November to March. Taking the 2003/2004 season as an example, this means that any children born from December 2001 to March 2004, a period of 28 months, may potentially be eligible for palivizumab.

Using this premise, the population-based Nova Scotia data were first used to calculate the expected proportion of children who would have been born with CHD (and thus potentially eligible for prophylaxis) during the immunization period. For the 2003/2004 season, that proportion was calculated as follows: the number of children with any potentially significant CHD diagnosed before they reached two years of age from December 2001 to March 2004 (identified in the pediatric cardiology database) was divided by the number of children born to Nova Scotian residents from December 2001 to March 2004 (identified from the Nova Scotia Atlee Perinatal Database – a prospective population database that lists all births in the province).

Because children with cardiac disease may be eligible for prophylaxis in two seasons, the concept of 'patient-seasons' of prophylaxis, rather than the absolute numbers of patients, must be used when applying this proportion to other provinces. One patient-season is a course of prophylaxis for one winter. The number of potential patient-seasons in each RSV season was calculated by multiplying the proportion above by the number of births in each 28-month period in each province. Provincial birth data were obtained from Statistics Canada. Because yearly birth numbers were the only ones available, an average number of births per month was calculated and used to determine the number of births in the four extra months in each season. This allowed the calculation of the expected number of potential patient-seasons for each RSV season in each province.

The proportion of potential patient-seasons expected to have hemodynamically significant CHD and have children who require prophylaxis was then calculated from the Nova Scotia data for each season. Using the 2003/2004 season as an example, the calculation would be as follows: the number of patient-seasons referred for immunization in Nova Scotia in 2003/2004 was divided by the number of potential patient-seasons (children with any potentially significant CHD diagnosed before they reached two years of age) from December 2001 to March 2004.

The proportions for both seasons were averaged to calculate the final proportion. Proportions are expressed as percentages (ie, multiplied by 100).

Using the proportions derived as above and the number of births for each province as provided by Statistics Canada, the expected number of children to have any form of CHD potentially requiring prophylaxis and the expected number of patient-seasons for prophylaxis were calculated. The calculated expected number of patient-seasons potentially requiring prophylaxis was used, along with the actual numbers prophylaxed, to calculate a percentage of children with CHD who actually received passive immunization.

The numbers of births in Nova Scotia during the time periods under study were obtained from the Nova Scotia Atlee Perinatal Database. This database contains prospectively entered data on all children born to Nova Scotian residents. The number of children diagnosed with CHD each year was obtained from the pediatric cardiology database at the IWK.

RESULTS

Four hundred one children younger than two years of age with a new diagnosis of cardiac disease, representing 545 potential patient-seasons of prophylaxis, were identified from the cardiology database in the first two years of the program. The Nova Scotia Atlee Perinatal Database recorded 20,173 births in Nova Scotia between December 2001 and March 2004; 19,227 births were recorded between December 2002 and

March 2005. Using these data, the proportion of potential patient-seasons was calculated as 13.8 per 1000 births. This proportion can be thought of as the number of children born with any form of CHD; it was used to calculate the expected number of patient-seasons in each province each year.

Over the two years, 14 children were identified through health record review at the start of each season. Seven additional patients were diagnosed with heart disease in the course of both seasons, referred for prophylaxis and immunized. Two children who had been identified in the first review were later removed from the list (before prophylaxis started, because their clinical condition had improved or their lesions had been repaired before the start of the season). This brought the total number of patient-seasons referred for immunization to 19, and allowed the calculation of the expected percentage of potential patient-seasons with hemodynamically significant CHD ($[19/545] \times 100 = 3.5\%$) and therefore needing prophylaxis.

Using the proportions above, the numbers of potential patient-seasons and the number of these expected to have hemodynamically significant heart disease in each season (number of expected patient-seasons) were calculated. To protect the confidentiality of each province, only the percentage of patient-seasons actually given palivizumab, compared with the expected percentage, is provided (Table 1). In most provinces, the percentage of children who received prophylaxis exceeded the percentage of children expected to be eligible in at least one of the seasons under study. Moreover, in all but two instances (one grouped), the percentage increased in the second season compared with the first.

DISCUSSION

The potential benefits of palivizumab immunization for children with CHD have been established (5). Like any expensive health care intervention, however, it must be used judiciously. We have shown that a provincially coordinated program ensures that all children at risk are given the opportunity to receive prophylaxis and avoids the inappropriate administration to lower-risk children. The availability of a comprehensive population-based cardiology database in Nova Scotia and the willingness of pediatric care providers to participate in this process have facilitated its functioning. Additionally, duplicate requests were intercepted and 'reshipment' was avoided, thus realizing further cost savings.

The comparison of the Nova Scotian data with those of other provinces showed that in most provinces, a higher percentage of patients with CHD were being immunized than was expected, based on current recommendations and population-based estimates of the prevalence of hemodynamically significant CHD (Table 1). In the provinces grouped, five of the eight percentages were higher than the Nova Scotian rates. Additionally, all but two provinces (one grouped) documented an increase in palivizumab use for cardiac indications in the second season of study compared with the first. Both of these situations have cost implications for governments and potential health implications for children. Although palivizumab is considered to be safe and serious adverse events following immunization are uncommon, such events do occur, and include allergic reactions and injection site pain (9).

Several formal costing studies, including a meta-analysis (10), have suggested that RSV immunization is not cost-effective. The only study of the cost-effectiveness of palivizumab use in

TABLE 1
Estimated provincial and territorial percentages of Canadian children younger than two years of age with cardiac disease receiving antirespiratory syncytial virus monoclonal antibody prophylaxis, compared with expected percentages

Province	Potential patient-seasons expected to be given prophylaxis, %	Potential patient-seasons that were actually given prophylaxis, %	
		2003/2004	2004/2005
A	3.5	3.5	5.3
B	3.5	4.3	6.1
C	3.5	6.7	11.0
D	3.5	7.3	6.2
E	3.5	6.4	8.2
F, G, H, I, J*	3.5	6.3	7.9
Quebec	3.5	6.1	unknown
Nova Scotia	3.5	3.5	3.5

*Five provinces grouped

children with CHD confirmed these findings (11). However, our data suggest that as many as 380 Canadian children may have received potentially unnecessary immunizations in the past season. This finding is in accordance with those of Bellavance et al (8), who estimated that 29 children in their series (nearly 20%) were given palivizumab unnecessarily. While a formal costing study is beyond the scope of the present paper, we argue that there are undoubtedly economic and patient safety benefits of avoiding the administration of an expensive humanized monoclonal antibody to ineligible children if a province decided to offer this prevention program. For example, in Nova Scotia, the product costs of palivizumab for cardiac indications in the province over the two seasons studied were \$122,562.05 (2003/2004) and \$50,639.41 (2004/2005), totalling \$173,201. Rejection of duplicate requests avoided shipping and saved \$14,678.10. The theoretical cost of immunizing all children with CHD (based on an average weight of 5 kg, with a 1 kg/month weight gain over the succeeding four months and a 15 mg/kg dose for 526 potential patient-seasons) is \$4,142,250. While there are many other considerations besides cost in clinical decision making, the careful use of resources must always be a consideration. We hope that our model of care delivery to children with cardiac disease will be of use to other jurisdictions who seek to optimize delivery of their RSV immunization programs.

A limitation of the present analysis includes the use of gross population estimates in the calculation of expected numbers of children requiring palivizumab prophylaxis in other provinces. The outcomes of interest (children with CHD and hemodynamically significant CHD) are also rare, such that a few additional cases may have a significant impact on the calculations. We have attempted to minimize this by using the average rate of CHD for the two seasons under study. Additionally, eligibility for prophylaxis changes over time, and prophylaxis is administered over a varying time period in different provinces. Our data cannot account for such practices. Children also are sometimes eligible for prophylaxis in more than one year. The proportions of patient-seasons calculated should, therefore, optimally be applied to children who are younger than two years of age during the prophylaxis period. In the present case,

the only data available were the yearly number of births. Because this figure is relatively constant, we chose to use it as the basis for our calculation; this would at least overestimate the number of patient-seasons expected in each province. However, in all cases, more patients were receiving prophylaxis than was expected.

CONCLUSIONS

The use of palivizumab in children with CHD can be optimized through a multidisciplinary provincial model in which children requiring prophylaxis are prospectively identified and reviewed by pediatric cardiologists. Such a model ensures that all patients requiring prophylaxis receive appropriate immunization, and avoids the monetary and health costs of the immunization of low-risk children with CHD, in whom the benefits of palivizumab have not been proven.

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