Reproductive Care Program of Nova Scotia
RCP
NEWSLETTER
Winter/Spring 2009

Ethnicity-Based Genetic Carrier Screening in the Maritime Provinces

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Maritime Medical Genetics

In many cases, the incidence of various genetic conditions varies between different ethnic groups. In the case of autosomal recessive conditions, this implies that the carrier rate for a particular condition also varies. In some populations, the carrier rate for specific mutations is significant enough, from a public health point of view, to justify the offering of genetic carrier screening to those groups. Ideally, couples who may benefit from ethnicity based carrier testing should be identified prior to a pregnancy or failing that, as early as possible in a pregnancy. Ideally, genetic counselling, and if subsequently requested by the patient, genetic testing, should be offered simultaneously to both partners. When this is not feasible, counselling can be given to the available partner. With the exception of the Haemoglobinopathies, genetic counselling need only be offered when partners are of the same at-risk ethnicity (or are from different ethnicities with increased carrier rates for the same condition). If a family history of a particular condition is present (either an affected family member or a known carrier), referral to medical genetics is generally indicated, irrespective of the other partner's ethnicity. Guidelines as to which specific populations in Canada should be screened for which conditions are fragmented and incomplete. To further add to the uncertainty, in many cases the Canadian guidelines provide different suggestions than corresponding guidelines from other sources [1,2].

At present, there are no formal guidelines specific to the Maritimes. With this absence in mind, based upon discussion with our colleagues in the Maritime Medical Genetics Centre, we would propose that prenatal ethnic carrier testing should be offered to the ethnic groups listed below. In making these suggestions, we have adhered to the Canadian guidelines and widely accepted criteria for when it is appropriate to offer genetic screening [3,4,5]. In particular we have only suggested testing for autosomal recessive conditions with severe life threatening presentations in childhood. With the exception of testing for the Haemoglobinopathies and biochemical testing for Tay-Sachs disease, we would only suggest testing for the individual mutations known to be carried at an increased incidence in the specific populations. We feel that the initial discussion regarding the conditions should begin in the primary care context. If a couple is interested in learning more about these conditions, their risks and the option of genetic testing, a referral to medical genetics should follow. To facilitate the initial discussion and allow patients to make informed decisions in the primary care venue, we list below the ethnicities for which consideration of genetic carrier screening should occur.

With the exception of the Haemoglobinopathies, the actual genetic or biochemical testing requires specific consents,

requisitions for out of province testing and arrangements for specimen handling. Failure to complete the necessary paperwork in its entirety or use of alternative requisitions frequently results in significant delays in testing or no testing at all. To alleviate these system related obstacles, it is our suggestion that all of the actual arrangements for genetic testing (with the exception of the initial screen for Haemoglobinopathies) be arranged via the Maritime Medical Genetics Clinic. In some instances, testing for certain ethnicities is only available out of province via fixed panels. This can make it necessary to screen for conditions which fall outside the following suggestions.

Inheritance

All of the conditions listed below are inherited in an autosomal recessive manner. Carriers of an autosomal recessive condition have a working copy of the gene and a non-working copy. In general, carriers of autosomal recessive conditions do not have symptoms and remain unaffected and therefore, unaware that they are carriers. Both parents must be carriers of the same condition to be at risk to have an affected child. In each pregnancy, parents who are carriers of the same autosomal recessive condition have a 1 in 4 (25%) chance to have a child who is affected with the condition.

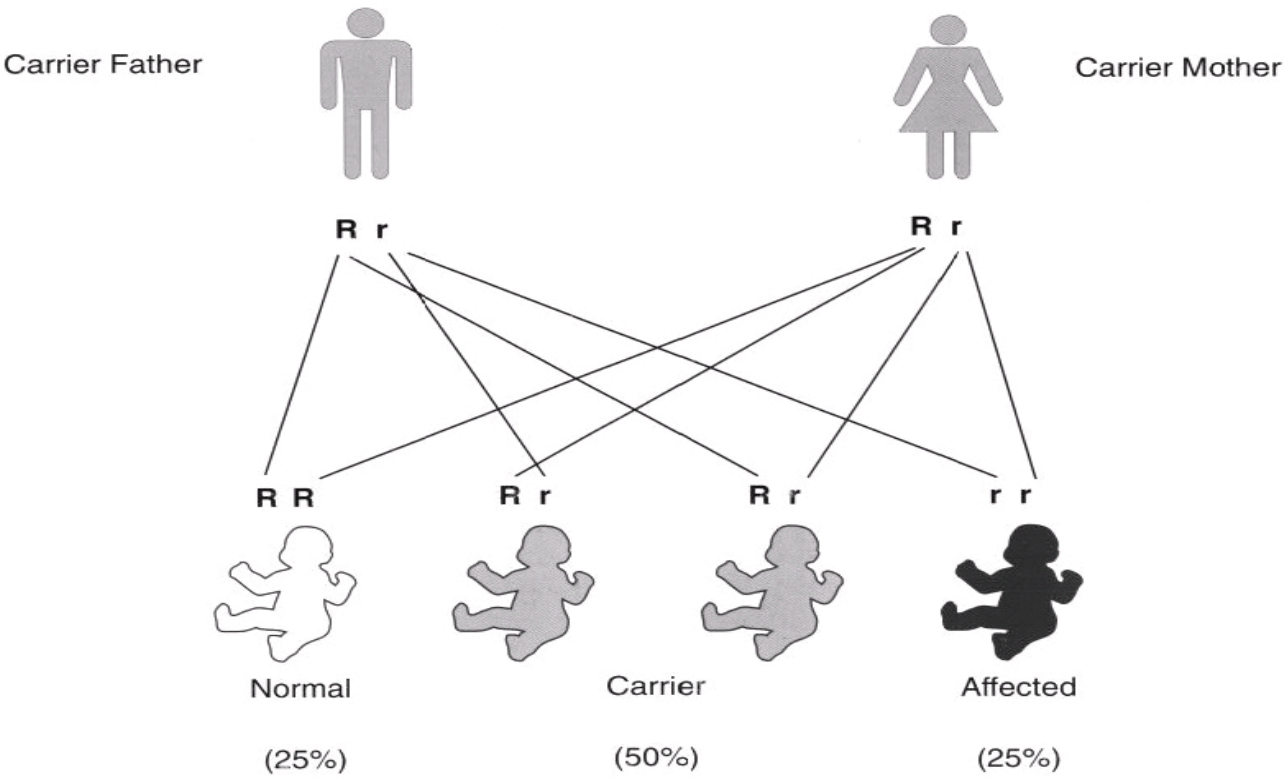


Figure 1. A family tree depicting autosomal recessive inheritance and risks to offspring (Counseling Aids for Geneticists, Greenwood Genetic Centre, 1995).

A. Conditions for Genetic Counselling and Testing in the Primary Care Environment

Haemoglobinopathies

Based upon the current Canadian College of Medical Geneticists (CCMG) and Society of Obstetricians and Gynecologists of Canada (SOGC) recommendations[4], if either partner is from an ethnicity with an increased carrier rate, at least one member of the couple should be screened. Ideally the partner at increased risk should be tested. Screening comprises both a complete blood count (CBC) and Haemoglobin electrophoresis. If the mean cellular volume (MCV) is less than 80fL or the mean cellular hemoglobin (MCH) <27pg, or the haemoglobin electrophoresis is abnormal, then the other partner should be screened as well. Both individuals should also have a haemoglobin H prep and iron deficiency anaemia should be ruled out. MCH is less affected than MCV by delays in testing completion.

Table 1. The ethnic carrier screening suggestions for Haemoglobinopathies

Ethnicities that should be screened for Haemoglobinopathies	
African	Sickle Cell Anaemia, Thalassemia
Asian (omitting Japan)	Thalassemia
Caribbean	Sickle Cell Anaemia, Thalassemia
Hispanic or Central/South American	Sickle Cell Anaemia, Thalassemia
Mediterranean (including Sephardic Jews)	Sickle Cell Anaemia, Thalassemia
Middle Eastern	Sickle Cell Anaemia, Thalassemia

Sickle Cell Anaemia causes chronic haemolysis causing **normocytic** anaemia, jaundice and gallstones. This condition also causes intermittent episodes of vascular occlusion resulting in acute and chronic damage to multiple organs, paroxysmal episodes of severe pain and predisposes to bacterial sepsis. There is an increased carrier frequency for Sickle Cell disease among individuals of African ancestry (in some countries the carrier rate approaches 30%) and to a lesser extent, Middle Eastern and Mediterranean descent. Screening for carriers is accomplished by haemoglobin electrophoresis, which reveals the presence of haemoglobin S. Although CBC's are usually normal in carriers (including MCV and/or MCH), it is still worthwhile to test to insure that the individuals do not carry another haemoglobinopathy.

Thalassemia causes severe anaemia and hepatosplenomegaly. It is due to reduced production of either beta or alpha globins, in beta- and alpha-Thalassemia respectively. Children born with beta-Thalassemia will generally be healthy at birth, but become anaemic as their fetal haemoglobin decreases during the first few months of life. Thereafter, severely affected children will require either bone marrow transplantation or life-long periodic blood transfusions and daily iron chelation. In severe cases of alpha-Thalassemia the affected pregnancy may become hydropic due to fetal anaemia. There is also an increased risk for other congenital abnormalities. Less severe presentations are compatible with life, but frequently require ongoing therapy. Carrier states of both alpha- and beta-Thalassemia are asymptomatic. Individuals of Mediterranean, Middle Eastern, African and Asian ancestry have an increased carrier frequency. In some populations the carrier rate for Thalassemia is over 10%.

In beta-Thalassemia carriers, the CBC will usually show low MCV or MCH (in the absence of iron deficiency) and high haemoglobin A2. In carriers of alpha-Thalassemia, either the MCV or MCH is low and the haemoglobin electrophoresis is normal, making differentiation from iron deficiency difficult. In all cases of non-iron deficiency related microcytic anaemia of unknown aetiology, referral to Medical Genetic for genetic testing for alpha-Thalassemia is indicated.

B. Conditions for Which Testing should be performed following referral to Medical Genetics

Table 2. The ethnic carrier screening suggestions for individuals of Ashkenazi Jewish, Bas-St-Laurent French, Saguenay-Lac-St-Jean French, and Yarmouth and Arichat County Acadian and Eskasoni First Nations ancestry.

Suggested Screening for Specific Ethnicities	
Ashkenazi Jewish	Canavan, Familial Dysautonomia, Tay-Sachs
Bas-St-Laurent French	Tay-Sachs
Saguenay-Lac-St-Jean French	ARSACS, COX-SLSJ, Cystic Fibrosis, HMSN, Tyrosinemia
Yarmouth County Acadian	Alström, Niemann-Pick type C
Arichat/Louisdale region Acadian	Metachromatic Leukodystrophy
Eskasoni First Nations	Severe Combined Immunodeficiency

Ashkenazi Jewish

Much controversy exists as to which conditions should be screened for. In particular, American guidelines suggest screening for many more conditions than is the accepted norm in Canada. The primary Canadian guideline suggests only screening for Tay-Sachs, Canavan and Familial Dysautonomia (Riley-Day syndrome) [1]. Some Canadian Centres also suggest screening for Cystic Fibrosis. Testing for Gaucher disease is also offered in some centres based upon the high carrier rate, but such screening is controversial as a significant subset of homozygous individuals in this population do not develop symptoms until late adulthood. For the Maritimes, we generally suggest adhering to the current CCMG guidelines. If couples wish to discus screening for further conditions, referral to Medical Genetics is indicated.

Canavan disease is a neurodegenerative disease. Symptoms generally develop by 3-5 months of age, presenting with macrocephaly and hypotonia. Later developmental delay develops as well as spasticity. Sleep disturbances, seizures and feeding difficulties are not infrequent in later years. Death usually occurs within the first two decades of life. The carrier frequency in the Ashkenazi Jewish population is $^{1}/_{40}$.

Familial Dysautonomia (Riley-Day syndrome) is a progressive condition with symptoms that may present at birth. It causes progressive degeneration of the sensory, sympathetic and parasympathetic neurons. Individuals lose the ability to feel pain or temperature changes and have feeding and movement difficulties. Life expectancy is reduced. The carrier frequency in the Ashkenazi Jewish population is $^1/_{36}$.

Tay-Sachs disease is a lysosomal storage disease that causes a progressive neurological degeneration with onset by 3-6 months of age. There is progressive deterioration leading to seizures, blindness, and paralysis and death by 4-6 years of age. There is currently no treatment. The carrier frequency in the Ashkenazi Jewish population is $^1/_{31}$.

Bas-St-Laurent French Canadian

Tay-Sachs disease has a similar presentation in this ethnic group as it does in Ashkenazi Jewish individuals. The exact carrier frequency among French-Canadians from this region is unknown, but is believed to be significantly increased. The carrier rate in other regions of Quebec may also be higher, but is likely not increased enough that screening is indicated.

Saguenay-Lac-St-Jean French Canadian

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) causes progressive spastic ataxia starting in infancy that can progress to paraplegia. Individuals usually require a wheelchair by 41 years of age and typically pass away in their 6th decade of life. The carrier frequency in the Saguenay-Lac-St-Jean (SLSJ) region is $^1/_{22}$.

Cytochrome c Oxidase Deficiency, Saguenay-Lac-St-Jean type (COX-SLSJ) is a severe condition with a high infantile mortality rate due to episodes of severe acidosis and coma. Individuals also have developmental delay, hypotonia, and may have dysmorphic facial features. The carrier frequency in the SLSJ region is $^1/_{23}$.

Cystic Fibrosis (CF) is a condition that primarily affects the lungs and the digestive system through the production of thick mucus. The mucus production can also affect both male and female fertility. The average age of survival in individuals with CF is 37 years. The carrier frequency in individuals from SLSJ region is $^1/_{15}$.

Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum (HMSN-ACC) causes progressive neurodegenerative with symptoms becoming apparent in infancy. Infants have absent reflexes, hypotonia and limb weakness. Patients are often wheelchair bound by 14 years of age and often pass away by 33 years of age. The carrier frequency in the SLSJ region is $^1/_{23}$.

Tyrosinemia type 1 is an inborn error of metabolism associated with progressive liver damage and renal tubular acidosis. If untreated, death usually occurs with the first decade. Recently, treatment has become available, which when combined with a strict diet appears to ameliorate many of these symptoms. Treatment is intensive and life-long; long-term outcome studies are not yet available. The carrier frequency in the SLSJ region is $^{1}/_{21}$.

Yarmouth County Acadian

Alström syndrome is a condition with multisystem organ involvement, with symptoms becoming apparent in infancy. Among the earliest symptoms are a cone-rod dystrophy (which can result in nystagmus and leads to eventual blindness), sensorineural hearing loss, and dilated cardiomyopathy. Over time affected individuals often become obese, develop insulin resistance and progressive renal damage. Life expectancy is often significantly shortened. Alström syndrome is a rare condition with approximately 300 reported cases of the condition worldwide. A significant proportion of those affected have been of Acadian ancestry, with most cases occurring in individuals from Yarmouth County. Carrier rate unknown, but may well be high enough to justify carrier screening. Studies of carrier rates are ongoing, and in the interim we suggest that carrier testing be offered.

Niemann-Pick type C disease is a neurodegenerative multisystem condition. Developmental regression usually begins in the first decade of life. Seizures frequently develop and death usually occurs in the 2nd to 3rd decade of life. This condition can also cause fetal ascites and neonatal jaundice, which may be transient. The carrier rate in this population is unknown, but may well be high enough to justify carrier screening. Studies of carrier rates are ongoing, and in the interim we suggest that carrier testing be offered.

Arichat/Louisdale region Acadians

Metachromatic Leukodystrophy (arylsulphatase deficiency), the infantile form, is found at an increased incidence in Acadians from the Arichat/Louisdale area of Cape Breton. Affected infants have progressive developmental delay and neuropathy. Later in the disease course, hypertonia and spasticity develop. Affected children usually come to medical attention between 1-2 years of age and death usually occurs by 5 years. The carrier rate in this population is unknown, but may well be high enough to justify carrier screening. Studies of carrier rates are ongoing, and in the interim we suggest that carrier testing be offered.

Eskasoni First Nations

Severe Combined Immuno Deficiency due to Rag-2 deficiency presents in affected infants by 3 to 6 months of age once transplacentally transfused maternal antibodies have been depleted. Repeat infections may initially seem ordinary (e.g. pneumococcus, RSV, or otitis media), however they tend to not respond to standard treatment and to

reoccur. If untreated, affected children usually die within the first year of life. Treatment regimes include prophylaxis and early detection, with most individuals requiring a bone marrow transplantation. The carrier rate for this condition in this population is unknown, but is likely high enough to justify the offering of genetic screening.

1) Langlois S, Wilson R, et al. Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada & Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists Carrier screening for genetic disorders in individuals of Ashkenazi Jewish descent. J Obstet Gynaecol Can 2006; 28: 324–343.

2) Gross SJ, Pletcher BA, Monaghan KG. Carrier Screening in Individuals of Ashkenazi Jewish Descent. ACMG Practise Guideline. Genetics in Medicine 2008; 10(1): 54-56.

3) Chodirker BN, Cadrin C, Davies GAL, Summers AM, Wilson RD, Winsor EJT, Young D, et al. Canadian guidelines for prenatal diagnosis. Genetic indications for prenatal diagnosis. SOGC Clinical Practice Guideline No. 105. J Soc Obstet Gynaecol Can 2001; 23: 525–31.

4) Langlois S, Ford JC, Chitayat D, Desilets VA, Farrell SA, Geraghty M, Nelson T, Nikkel SM, Shugar A, Skidmore D. Carrier Screening for Thalassemia and Hemoglobinopathies in Canada. Joint SOGC-CCMG Clinical Practice Guideline No. 218. J Soc Obstet Gynaecol Can 2008; 218: 950–9.

5) Khoury MJ, McCabe LL, McCabe ERB. Population screening in the age of genomic medicine. New Engl J Med 2003; 348: 50–8.

New Data Collection Processes for Midwifery Care in Nova Scotia

As of March 18th 2009, midwifes became legislated and regulated maternity and newborn health care providers in Nova Scotia. This is a very exciting time for women, families and all health care professionals.

The integration of this new health care provider will start with 3 pilot sites, Guysborough-Antigonish Strait District Health Authority, South Shore District Health Authority and the IWK Health Centre. Each pilot site has been working very hard to create implementation and integration programs so that midwives may begin practice in April 2009. Each model site may look a bit different depending on the needs of the community.

As with any change in health care practice, comes a change in the data collection process. Data collection changes related to midwifery care include a plan for gathering information on home births and changes to the definitions of delivery physician and attending physician in the coding manual to include midwives. We will have a provider number in the List of Values for deliveries attended by a midwife. The plan is to capture a home birth as a delivered case as if it occurred within the facility. I will be sending out a much more detailed account of data collection procedures for midwifery deliveries with the April 1, 2009 discharge changes.

Thank you in advance for all your patience as we prepare to send out the changes for the April 1, 2009 data collection process. Many of these changes reflect feedback we've received from Health Information Professionals throughout the province who collect RCP information.

Have a great spring and summer,
Irene
Irene.gagnon@iwk.nshealth.ca

Implementing the CPS Hyperbilirubinemia Position Statement in Nova Scotia

Introduction

The RCP invited representatives from around Nova Scotia to be part of a Working Group to consider strategies for implementing the **CPS Guidelines for Detection, Management and Prevention of Hyperbilirubinemia** that were released in 2007. These guidelines apply to all healthy Nova Scotia newborns who are at least 35 weeks gestation at birth, and include recommendations with implications for the newborns, their families, and those who provide their care.

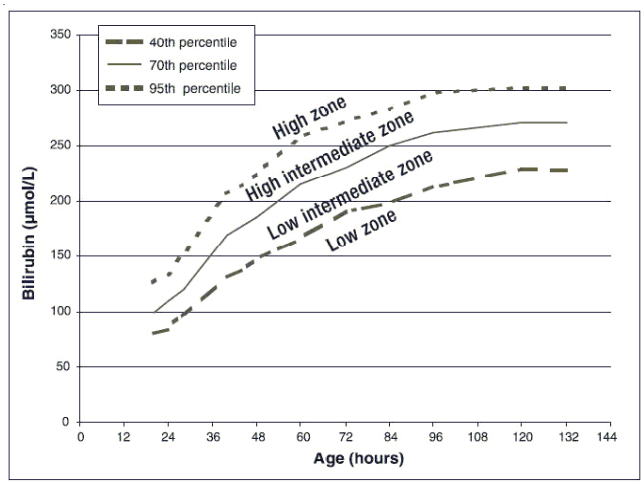
Hyperbilirubinemia is a transitional phenomenon occurring in approximately 60% of term infants and virtually all preterm infants (CPS, 2007). Bilirubin normally peaks at 3 to 5 days of life. The guidelines were developed by CPS because of concerns about the rare but catastrophic neurological effects of *critical* hyperbilirubinemia i.e. total serum bilirubin (TSB) > 425 µmol/L, and the possibility that bilirubin levels might increase to this level undetected, particularly if hospital discharge has already occurred.

CPS Recommendation

The CPS recommends that all babies have a bilirubin measurement obtained when jaundice is observed, or routinely within the first 72 hours of life. A routine serum test is preferably drawn with the metabolic screen.

(Note: The CPS has suggested that either a serum or transcutaneous bilirubin measurement is appropriate. The NS Working Group has *not* recommended that facilities purchase transcutaneous bilirubinometers for screening if not already using these devices. These instruments are costly and reportedly subject to considerable inter-operator variability.

If treatment is not required, the result should be plotted on the 'predictive nomogram' against the age of the baby at the time the bilirubin was drawn.



Reprinted from CPS Position Statement, 2007

Interpretation

Results will fall into one of 4 'zones'. These zones help predict which newborns are more likely to develop *severe* hyperbilirubinemia i.e. TSB > 340 µmol/L, and to suggest what level of follow-up care is appropriate to prevent a continued bilirubin increase to an unsafe level. Bilirubin results should be considered in the context of gestational age and Direct Antibody Test (DAT). Babies who are late preterm, i.e. born at 35 to 37 6/7 weeks gestation, and/or with a positive DAT have greater risk of developing severe hyperbilirubinemia. A DAT is not required for every baby. In addition to cases where there are positive or unknown maternal red blood cell (RBC) antibodies, a DAT is indicated for those babies with risk factors for severe hyperbilirubinemia such as early jaundice, results plotting in the high or high intermediate zone, and gestations less than or equal to 37 6/7 weeks.

The following chart was adapted from the CPS guidelines by the NS Working Group to assist with interpretation of the TSB results.

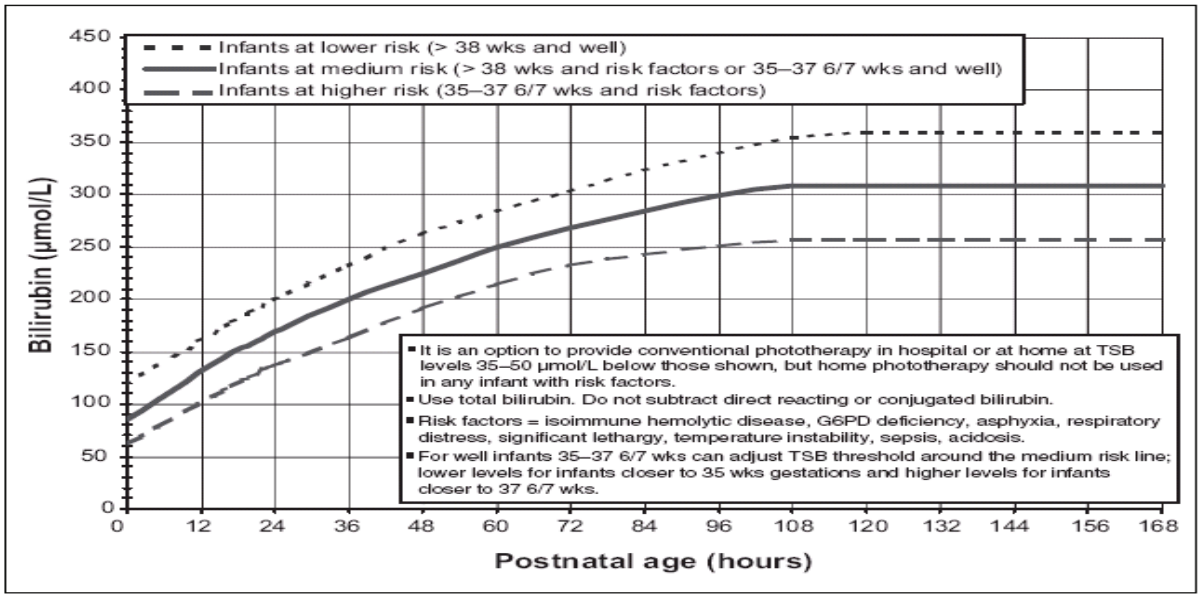
	> 38 weeks and DAT* neg	> 38 weeks and DAT* pos	35-37/6/7 weeks and DAT* neg	35-37/6/7 weeks and DAT* pos
High	Further testing or Rx	Further testing or RX	Further testing or Rx	Phototherapy
High-Intermediate	Routine Care	Follow-up within 24-48 hours	Follow-up within 24-48 hours	Further testing or treatment
Low-Intermediate	Routine Care	Routine Care	Routine Care	Further testing or treatment
Low	Routine Care	Routine Care	Routine Care	Routine Care

* if DAT indicated

Treatment and follow-up

Phototherapy is the recommended treatment for hyperbilirubinemia. Decisions about initiating phototherapy are made by plotting the bilirubin results on a treatment graph against the age of the baby at the time the TSB was obtained. To decide about treatment, clinicians must also consider risk factors such as visible jaundice, gestation < 37 6/7 weeks.

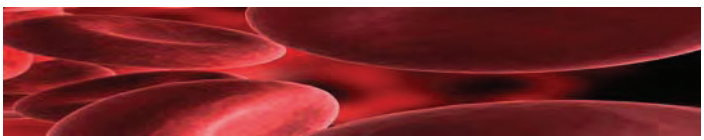
The CPS guidelines include a treatment graph for 'intensive phototherapy' (see graph). Intensive phototherapy can be provided using two phototherapy units each with intensity of > 30 µW/cm^2/nm and placed approximately 10 cm from the baby. 'Conventional phototherapy', generally involving a single phototherapy unit, may be considered for babies with moderate risk of developing severe hyperbilirubinemia and a bilirubin level 35 µmol/L to 50 µmol/L below those levels indicated on the 'intensive' graph. If the TSB continues to increase toward the critical level in spite of intensive phototherapy, consultation with a neonatologist regarding exchange transfusion should be arranged.



If phototherapy is not required but the baby's bilirubin level falls into a zone that indicates the need for further testing or follow-up, a repeat bilirubin level should be obtained as early as 24 hours or within 24 to 48 hours. It will be essential for health professionals in each district to identify a process, prior to discharge, that facilitates repeat testing and ensures that results are forwarded to the responsible primary care provider. CPS recommends that this testing continue until the bilirubin level begins to fall and until weight gain and feeding are well established. Parents need to be informed of the method of testing, the rationale for the CPS recommendation, and the importance of follow-up.

In addition to repeat testing, follow-up should include an assessment of the infant, and an evaluation of feeding. The CPS discourages routine supplementation of breastfed infants however does recommend that skilled breastfeeding support be accessible both in hospital and following discharge.

In the following weeks, materials developed to assist districts with implementation of these guidelines will be distributed to neonatologists, pediatricians, primary care providers (i.e. family physicians, midwives, and nurse practitioners), Maternal Newborn Nursing Units and Public Health Offices around the province.For more details please refer to CPS at www.cps.org, the RCP website at http://rcp.nshealth.ca or contact Martha Nutbrown at martha.nutbrown@iwk.nshealth.



CONFERENCES & EVENTS

SOGC (Society of Obstetricians & Gynecologists of Canada) annual clinical meeting will be held June 17-21, 2009 in Halifax, NS. Please see the website at www.sogc.ca for further details.

CPS (Canadian Pediatric Society) annual conference will be held June 23-27, 2009 in Ottawa, Ontario. Please see the website at www.cps.ca for further details.

The **CPPC** (Canadian Perinatal Programs Coalition) meeting will be June 16, 2009 and the **CPDC** (Canadian Perinatal Database Committee) meeting will be held June 15, 2009, both in Halifax, NS. For further information, please contact Marilyn Muise at marilyn.muise @iwk.nshealth.ca

The **AWHONN** (Association of Women's Health Obstetric, Neonatal Nurses) **Canada 20th National Conference** will be held October 15th-17th, 2009 in Winnipeg, Manitoba. For further information please see the website at:www.awhonncanada.org

The next **ALSO (Advanced Life Support in Obstetrics)** course will be held May 9th and 10th at the Cape Breton Regional Hospital in Sydney, Cape Breton, NS. Space is limited so register early. Please check the RCP website for more information.

There will be another ALSO course at the IWK Health Centre in Halifax, NS, November 28th and 29th, 2009. Details will be posted on the RCP website in the near future. For more information please contact Marilyn Muise at marilyn.muise@iwk.nshealth.ca

The next Acute Care of the at-Risk Newborn (ACORN) course will be held April 24th and 25th, 2009 at the Colchester Regional Hospital in Truro, NS. For more information please contact Martha Nutbrown at martha.nutbrown@iwk.nshealth.ca

The 2009 annual conference of the **Canadian Public Health Association** will be held June 7th-10th, 2009 in Winnipeg, Manitoba. Please see the website for more details. http://www.cpha.ca/en/conferences/conf2009.aspx

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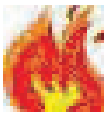
INTERESTING ARTICLE!

Gigerenzer,G., Gaissmaier, W., Kurz-Mileke,E., Schwartz, L. & Woloshin, S.Helping Doctors and Patients Make Sense of Health Statistics. *Psychological Science in the Public Interest, 8* (2), 53-96.

A **Warm Welcome to Leeanne Lauzon,** who joined the RCP team in October 2008 as a new Perinatal Nurse Consultant.

A **Fond Farewell to Jenny Whyte,** Applications Coordinator with RCP, who retired in October 2008.
Best Wishes, Jenny!

HOT OFF THE PRESS!



The new Fetal Health Surveillance manual is now available to order.

This manual is used to prepare participants with the fundamental knowledge about intermittent auscultation (IA), and electronic fetal monitoring (EFM), usually as a self-learning activity in preparation for a course. Nine authors from the disciplines of nursing, medicine and midwifery have contributed to the revision of this manual. There was also an extensive peer review process. All the authors and reviewers are acknowledged in the book. The chapters have been updated to reflect the new SOGC terminology and guidelines and a new chapter on non-stress test (NST) has been added. Additionally, tracings at 1, 2 and 3 cm/min have been introduced to meet everyone's learning needs.

Orders can now be placed with the British Columbia Perinatal Health Program (BCPHP).

The order form and instructions can be found at http://www.bcphp.ca/Fetal%20Health%20Surveillance.htm

To submit articles or photos for the next newsletter please contact Annette Ryan at (902) 470-6619 or annette.ryan@iwk.nshealth.ca by August 30, 2009