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# UTMJ

University of Toronto Medical Journal

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# Canadian Health Care:

Models of Economic Evaluation in Health Care

Student-driven Community Health Initiatives

The future of the Canadian Resident Matching Service (CaRMS)

Suicide in the Young and the Elderly

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# Table of Contents



***Cover Artist: Diana Kryski, HBA.*** Kryski received her undergraduate degree in Visual Studies and French as a Second Language from the University of Toronto, and is currently completing a Master's degree in Biomedical Communications in the Faculty of Medicine at U of T. Her research project involves the development and evaluation of a Flash-based learning tool aimed at enhancing medical students' spatial understanding of the pterygopalatine fossa and related skull cavities.

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The Editors apologize for any omissions to the above list; this list represents our final version at press time. We will update the list in future issues.

# Preface from the Editors

As the new Editors-in-Chief of the University of Toronto Medical Journal for 2007-2008, we are honoured to bring you the first issue of the year.

This year marks the UTMJ's 85th anniversary. We are greatly indebted to the editors and readers, both past and present. You have all been integral to the success of this unique journal for medical students. In our 85th anniversary edition coming up, we will feature a retrospective look at where we have been and where we are going. Medicine has changed substantially in 85 years, with the move towards personalized care, an emphasis on quality of life, and an increase in the use of technology. Through it all, as North America's oldest, student-run medical journal, the UTMJ has been there to present these issues and how they relate to the practice of medicine as seen by students and trainees. This year, we have added a 'Letters to the Editor' section to promote feedback and discussion. If you would like to share a comment on an article, please feel free to send it our way (editors.utmj@utoronto.ca).

The theme for this particular issue is Canadian health and the health-care system. As we grapple with changing health-care needs and methods of providing health-care, we hope that this issue will shed some light on the current situation. Ricketts and Sharma present two articles on the subject of suicide in Canadian adolescents and seniors, respectively. It is sobering to note that the suicide rate among senior men aged 75 yrs and over is comparable to that for young men aged 20-29 yrs at 30 in 100 000, both of which are more than twice the national average of 12 in 100 000. Both articles discuss risk factors for suicidal behaviour, treatment considerations, and increase awareness of this devastating disease. Also in this issue is a timely article by Smith discussing the ethical and legislative issues surrounding the recent HPV vaccine, which as of this Fall is being provided in public schools across Ontario and other provinces. Currently, 4th year clerks are applying to residency programs through CaRMS, the Canadian Resident Matching Service. Koo and Le interview Dr. Sarita Verma, the Chair of CaRMS and Vice-Dean of Postgraduate Education at the Faculty of Medicine at the University of Toronto, to talk about issues affecting residents and the changes being undertaken to help them in their training.

Lastly, we would like to give many thanks to our dedicated patrons and benefactors for their continued support and interest in this student journal.

We truly hope you will enjoy reading this issue of the UTMJ.

Sincerely,

*Sagar Dugani and Jonathan So*
Editors-in-Chief

# Shaken Baby Syndrome

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Work funded in part by Brandan's Eye Research Fund

Shaken Baby syndrome (SBS) is a severe form of child abuse that is associated with significant mortality and devastating long-term sequelae. It is characterized by the triad of encephalopathy, subdural hemorrhages, and retinal hemorrhage, with or without significant head injury. In July of 2005, successful appeals made to Britain's Court of Appeals generated much controversy with respect to the medicolegal definitions of SBS. In follow-up to the article "Shaken Baby Syndrome: The Debate Rages On"[1], we present the following corrections and updates:

The Baath article had incorrectly suggested that the successful appeals in 2005, of the three cases presented to Britain's Supreme Court of Judicature Court of Appeal (Criminal Division)[2], was evidence that SBS is not a form of child abuse. In fact, for one of the three cases, the defendant was still guilty of child abuse although the crime was downgraded from first-degree murder to manslaughter. For the other two cases, the appeals were upheld on the basis of legal technicalities during jury instructions. For example, in one case, where the child suffered injuries inconsistent with the history of a single accidental fall, the appeals court ruled that the jury had been incorrectly instructed to evaluate the case as SBS rather than abusive impact trauma. The judges further emphasized the validity of the triad of symptoms found in SBS.[3]

In attempting to challenge the notion of SBS as a medical reality, the defense referred mainly to the neuropathological study by Geddes *et al*, which argued that global hypoxic damage and eventual brain swelling can lead to bleeding that mimics the presentation of SBS.[4] This theory challenges the current understanding that attributes SBS injuries to the repetitive acceleration-deceleration shearing forces caused by shaking. This leads to the rupture of bridging veins in the cranium, and the disruption of retinal vasculature at the pediatric vitreoretinal junction.[5,6] Moreover, upon cross-examination by the crown, Dr. Geddes doubted the validity of her own hypothesis and believed that she would be "very unhappy to think that cases were being thrown out on the basis that [her] theory was fact."[2,3]

Similarly, other challenges to the authenticity of SBS as a form of child abuse have been disqualified**.** In the previous commentary by Baath, a reference was made to a single case report by Weedn *et al* of a child whose retinal hemorrhage (a sign associated with SBS) may be attributed to cardiopulmonary resuscitations (CPR). The child died from hot water burns, who at autopsy had "several large patches of retinal hemorrhages situated in the nerve fiber layer in the equator and posterior pole of both eyes".[9] Studies have demonstrated that CPR rarely cause retinal hemorrhages; and when it does, the hemorrhages are few in number and confined to the posterior pole. This is unlike the extensive, often confluent, subretinal, intraretinal and preretinal hemorrhages extending to the peripheral retinal edge (ora serrata) in two thirds of SBS cases.[5-8] In line with these studies, photographs accompanying the Weedn study only showed punctate retinal hemorrhage in the posterior pole, uncharacteristic of the extensive damage seen with SBS. In addition, this rare incidence of CPR-related retinal hemorrhage may be a compound effect of the concurrent medical complications of the child, including sepsis, severe hypoxia, hypotension, cerebral edema, and difficult intubation. Lastly, the hematologic status of the child remains unclear.

The link between head injuries and hemorrhagic retinopathy has also been raised, and remains controversial. Plunkett[10] suggested that fatal pediatric head injuries due to short distance falls could cause hemorrhagic retinopathies mimicking the ocular findings of SBS. However, the study remains unrepresentative of the vast literature.[11-13] More recently, Lantz *et al*[14] and Lueder *et al*[15] reported severe hemorrhagic retinopathy in a child with a head crush injury. However, *Gnanaraj et al.* found that although retinal hemorrhages can be seen in accidental crush injuries to the pediatric head, severe hemorrhagic retinopathy was not observed.[16] Of course, the obvious history and supporting physical evidence in these accidental crush cases makes them easy to distinguish from SBS.

The adversarial nature of the criminal legal system is disposed to scrutiny and disputes. The court's ruling that the triad of encephalopathy, subdural hemorrhages, and retinal hemorrhage is not 100% diagnostic of SBS, is influenced by the testimony of a selected group of defense witnesses, whose opinions do not necessarily reflect those of the general scientific community. Although some questions about exact pathophysiologic and biomechanical mechanisms remain, the American Academy of Pediatrics,[17] American Association of Pediatric Ophthalmology and Strabismus, National Association of Medical Examiners[18] and American Academy of Ophthalmology[19] and many other organizations worldwide have published statements defining SBS. Moreover, articles defining and characterizing SBS have appeared in innumerable medical journals of various specialties, in many countries. In conclusion, the Appeals' Court's decision should not be used to undermine the significance of SBS.

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# What Models are used for Economic Evaluations in Health Care? What They do and What They Don't: A Review

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**Abstract**

Models are frequently used in economic evaluations to explain or predict the effects and associated costs of a health intervention on a particular population. Traditionally, the types of models that have been used are mathematical, regression and decision tree models. More recently, Bayesian models have also been employed. In this article, the methodology and applications of Bayesian models are compared with those of traditional models. Bayesian models offer several advantages over traditional models; however, given that each model has its own merits and demerits, it was concluded that for a particular application, the most appropriate model would be the one that most accurately represents the real life situations under investigation. When a single model is either too simple (leaves out well-understood effects) or too complex (includes vaguely understood effects), a hybrid approach may be appropriate.

## What is a model?

A model represents the understanding of a phenomenon that occurs in the real world. For any particular phenomenon, complex interactions may occur between the variables that contribute to it. These interactions may influence the nature of the phenomenon and its related outcomes. Each type of model makes it possible to understand certain interactions that may not be understood using another model. Thus, one can attempt to understand a complex phenomenon by breaking it down into simpler models. Models are used in all disciplines to explain or predict outcomes; for example, they are used to forecast weather, to set insurance premiums and to facilitate decision making for priority setting and resource allocation.

Recently, Bayesian models have been used to an increasing extent.[1,2,3,4] In particular, these models are used to determine cost-effectiveness of interventions by measuring their effects on health outcomes. Traditionally, mathematical, regression and decision tree models have been used for this purpose, and thus most individuals lack an understanding of the more recent Bayesian methods. There is a need to familiarize general readers with Bayesian models[5] in relation to traditional models. Here, the methodology of traditional and Bayesian models will be described in the context of the Ontario Prehospital Advanced Life Support (OPALS) study, which estimated the cost effectiveness of automated external defibrillators (AEDs) in improving survival in patients who experienced an out-of-hospital cardiac arrest.[6]

## MATHEMATICAL MODELS

### Simple Model

A simple mathematical model is one that uses arithmetic and algebra. This type of model is commonly used in health economics to estimate the cost effectiveness of an intervention in a group of patients relative to a control intervention in a similar group of patients.

Cost effectiveness of an intervention is determined by calculating the incremental cost effectiveness ratio (ICER), which is the ratio of the difference in costs ($\Delta C$) and difference in effects ($\Delta E$) between the intervention and control groups (i.e. ICER = $\Delta C/\Delta E$). Uncertainty around this estimate can be accounted for by sensitivity analyses, which could require recalculation of the ratio for the worst (pessimistic) and best (optimistic) scenarios.

For example, the OPALS investigators estimated that the rate of out-of-hospital cardiac arrest was 59 per 100,000 people (mean age = 70 years) in Ontario, and that 3.9% (183/4690) of cardiac arrest patients survived to hospital discharge.[7] However, they estimated that after the implementation of the automated external defibrillator (AED) program, in which responders to the '911' system carried AEDs and helped in resuscitating cardiac arrest patients, the survival rate was 5.2% (85/1641).[8] The odds ratio (OR) was 1.33 (95% confidence interval = 1.05, 1.70) for survival after implementation of the AED program relative to survival before implementation. In addition, the OPALS investigators estimated that the ongoing annual costs for continuing the AED program in Ontario would be $2,000 per 100,000 residents, or $2,400 per life saved.

This estimate of cost effectiveness is based on simple arithmetic. That is, in a population of approximately 13 million people in Ontario, there would be 7,670 annual cardiac arrests (59 arrests/100000 people EMBED Equation.[3] 13 million people), and thus approximately 100 additional lives (0.052-0.039 EMBED Equation.[3] 7670) could be annually saved by the ongoing AED program – this would correspond to $2,400 per life saved ($240,000/100 lives).

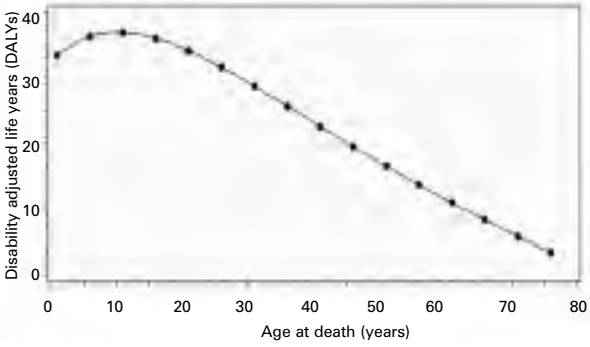
Assuming that the cost would vary from $1,000 to $3,000 per 100,000 residents and effectiveness would vary from 50 to

150 additional lives saved, the cost per life saved would range from $800 to $7,200 per life saved in the best and worst case scenarios, respectively.

A variation in this approach is what is called the cost utility analysis, which takes both the quantity and quality of life into consideration when measuring the health effect. This is done to account for the lower life expectancy and functional level of older individuals in comparison to younger individuals. Thus, the effect is expressed as the gain in quality-adjusted life years (QALYs). Assuming that the life expectancy at age 70 is 15 years, and that a person of this age functions at 80% of the functional level of a younger individual (e.g. a 25-year-old), each life of a cardiac arrest patient that is saved would correspond to an average gain of 12 QALYs (15 life years EMBED Equation.[3] 0.8 utility). Thus, the mean cost per QALY gained by the ongoing AED program would be $200 ($2,400/12 QALYs).

The advantage of this model is that it describes an otherwise complex phenomenon through simple and easily understandable arithmetic. The major disadvantage is that it does not capture the effect of response time, which is essential in improving survival through early cardiorespiratory resuscitation and defibrillation.[9]

### Complex Models




DALY has five components: duration of time lost due to a death at each age, disability weights (0 = perfect health, 1 = dead), age-weighting function, discounting function and cumulative value of health. These components are integrated in the DALY equation which produces the motion and change shown above.

**Figure 1.** Motion and change produced by a complex mathematical model

A complex implementation of mathematical models uses advanced mathematics (e.g. calculus, differential equations and difference equations). This may capture the motion and change that occur over time.

For example, Schlessinger and Eddy used difference equations to capture the events happening to a cohort of subjects during transition from one health state to another, allowing new subjects to enter the cohort during follow up.[10] They designed software called 'Archimedes', which has modeled outcomes for diabetes patients and has replicated several trial results.[11,12] Due to the complex equations underlying their model, they could not transparently describe their methodology; this has limited the acceptance of their work.[13] Archimedes was used to estimate the cost effectiveness of interventions for diabetes;[14] however, it was felt that more transparency was needed for the model to be used in informing policy decisions.[15]

Another application of advanced mathematics to economic modeling is the calculation of disability adjusted life years (DALYs), a measure of the number of life years lost due to premature disability or death. The DALY approach assigns higher value to life at young age, when people are economically more productive, than it does to life at the extremes of age. Thus, the death of an infant or elderly person is not weighted as heavily as that of a young adult.[16] This approach captures loss of productivity due to irreversible disability. In the DALY calculation, which was described by Homedes,[17] the parameters used are chosen arbitrarily. Nevertheless, **Figure** 1 illustrates the motion and change produced by the DALY equation in an age interval of 0–80 years. Here it is evident that DALYs lost tends to decrease as age increases.

When the DALY approach is applied to the ongoing AED program, it is found that 6.35 DALYs are saved if the death of a 70-year-old patient is averted. Thus, the mean cost per DALY saved would be $378 ($2,400/6.35 DALYs).

The advantage of complex models is that they capture longitudinal changes that may be non-linear. However, this advantage is offset by their complexity, which makes it difficult to describe them transparently.

### Regression Models

Regression models are generally used in analyses of data from observational and experimental studies. Their purpose is to explain or predict the effect of one or more variables on an outcome of interest. Using gathered data which contain values of predictors ($x$) and values of an outcome ($y$), all available observations are used to estimate the values of coefficients ($\alpha$,$\beta$) in a regression model ($y = \alpha + \beta x$). Since these models relate an outcome of interest to one or more predictor variables through regression coefficients, the outcome can be estimated for any given set of values of $\partial$, ß and $x$.

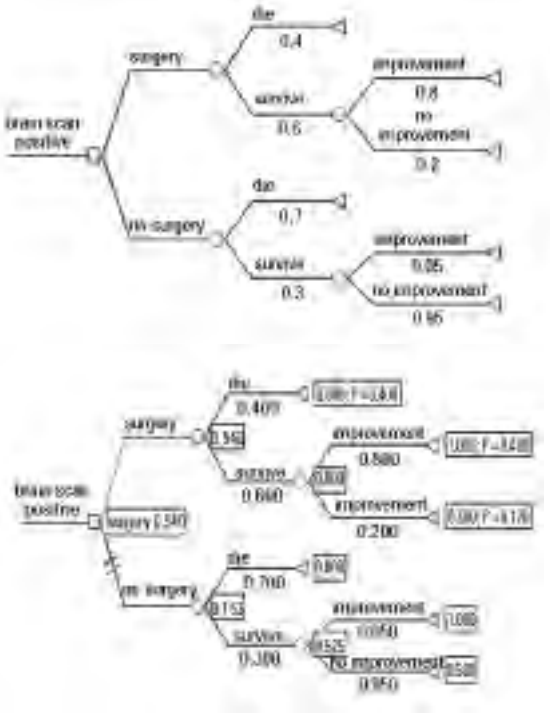
When the outcome is a binary variable, such as survival status (dead = 0, alive = 1), a form of regression called logistic regression is used. The OPALS investigators used this type of model to study the effect of response time on survival in cardiac arrest patients.[18] In their multivariable logistic regression model, the outcome was vital status at the time of hospital discharge, the predictor variable was defibrillation response time and the $\beta$ coefficient was -0.262. The antilog of $\beta$ yields the odds ratio of 0.77, which means that for each minute of delay in defibrillation from the onset of a cardiac arrest, the probability that the patient would survive to hospital discharge decreases by 23%. Conversely, it can be said that for each minute improvement in defibrillation response, the survival increases by 29% (1/0.77 = 1.29).

These estimates can be used to estimate the mean cost per life saved or mean cost per QALY gained as described previously. For example, if the current survival rate following cardiac arrest is 5.2%, and if the mean response time is reduced by 2 minutes, the survival rate would increase to 8.6% (5.2x1.29x1.29). This corresponds to 244 lives saved at a mean cost of $983 per life saved, or a mean cost of $82 per QALY gained.

There are several advantages to using regression models:

they are built directly from data, they employ standard and well-understood techniques, there is a large body of knowledge on model estimation and validation, and easy-to-use software for many types of regression models is readily available. Thus, descriptions of these models are easily communicated and widely accepted. Perhaps their main disadvantage is the potential 'abuse' of the current software packages that include automatic procedures for model selection. This tempts a novice to build a model without considering issues of model selection, model fit and validation, and such a model may not have any clinical utility.

### Decision Tree Models




A square indicates a decision node – the point where one decides which path to follow.
A circle represents a chance node – the point where one may experience one of the two outcomes to the right of the node.
A triangle represents a terminal node – an endpoint.
The diagram on the right shows expected values for each outcome depending upon which path is chosen and favors surgery over no surgery
Utility is 0 for death, 0.5 for no improvement and 1 for improvement

**Figure 2.** A simple decision tree

A decision tree model portrays the branching cascade of consequences that could arise from a decision, each consequence leading to one of several clinical scenarios.[19] At each level of the tree, the uncertainty around whether one branch or the other is taken is represented by a probability.[20] Associated with each clinical scenario is a utility, a global measure of health status expressed on a scale from 0 to 1, with 1 representing the best possible outcome (usually full health) and 0 representing the worst possible outcome (usually death).[21] Typically, values for probabilities and utilities are based on estimates (proportions, means and relative risks) from the literature.[22] The rational decision is the one that gives the maximum expected utility.[23] The strength of this modeling approach is that it can take into account the numerous potential benefits and harms resulting from each choice and thereby facilitate the process of making the best decision.

Consider an example of a patient whose brain scan is positive for the presence of a tumour. The patient has two options: elect for surgery, in which case there is a 60% chance of survival and an 80% chance of full functional recovery, or decline surgery, in which case there is a 30% chance of survival and a 5% chance of full functional recovery. **Figure 2** presents these scenarios as a decision tree using DATA 3.5™ (TreeAge Software, Inc. Williamstown, MA). This model assigns a utility of 0 to death, 0.5 to being alive with limited functional status and 1 to being alive with full functional status.[24] The expected value (EV) of the utility for a decision can be calculated by taking the product of the probability and utility of each branch for that decision and then finding the sum of these products. Thus, the EV of choosing surgery is 0.54 ([0 x 0.4] + [1 x 0.8 x 0.6] + [0.5 x 0.2 x 0.6]) and the EV of not choosing surgery is 0.15 ([0 x 0.7] + [1 x 0.05 x 0.3] + [0.5 x 0.95 x 0.3]). Based on these calculations, a rational decision maker would choose to undergo the surgery.

There is often uncertainty in the probability value assigned to a branch and in the utility assigned to a health state. For example, a probability based on published data will be known only to a certain level of precision. This uncertainty is addressed by carrying out sensitivity analyses using several plausible values for one or more components of the tree. For example, if the lower and upper boundaries of the 95% confidence interval for a probability correspond to 0.10 and 0.23 respectively, sensitivity analyses will involve two recalculations of EVs, replacing the value of the probability once with 0.10 and once with 0.23. If the optimal decision is the same for each of these analyses, the choice of best decision does not depend on knowing the exact value of the probability. If the two analyses give rise to different optimal decisions, then making the best choice requires more precise knowledge of that probability. An extension of this approach is to recalculate EVs many times for probabilities throughout their likely range. For example, values for the probability could be simulated using a normal distribution with mean 0.165 and standard deviation 0.0325, a so-called Monte Carlo simulation. For some of the simulated probabilities, the EV for one decision may be better and for others, the EV for the alternative decision may be better. If there is uncertainty for more than one component of the tree, this Monte Carlo simulation can be done simultaneously for all of them and the results can be summarized by computing the means (and their 95% confidence intervals) for each option. The rational decision would be the one that has the highest mean with the narrowest confidence interval.

Probabilities may change over time and thus standard decision tree models are not suited for modeling scenarios with long time horizons. For such applications, decision tree models are built as **Markov discrete-state** models.[25,26,27] A Markov Chain is a process that consists of a finite number of states and some known probabilities; the current status determines the probability of moving from one state to another in the next time cycle of the chain. The accompanying appendix provides

a working example of a Markov process using matrix multiplication.

Markov models make it possible to model health outcomes over a long time horizon while accounting for time-dependent changes in probabilities. Again, to better account for variation in the estimates of proportions and means, Monte Carlo simulations may be applied to a Markov model. For example, Nichol and colleagues used a Markov model to compare the potential cost-effectiveness of standard emergency medical service (EMS) with and without public-access defibrillators (PADs) available to lay responders and police officers.[28] The median incremental cost of adding PADs was $44,000 per QALY gained; for PADs made accessible to police officers, the cost was $27,200 per QALY gained.

One disadvantage of decision tree models is that they may overestimate the effects of a decision on quality of life measures when there are several co-existing conditions. Typically, in a decision tree, decrements in the utility value assigned to a given health state are the sum of individual decrements for components of that health state. For example, if a final health state consisted of four co-morbidities each associated with a 0.1 decrease in utility when compared to full health, the utility assigned to that health state would be 0.6. In practice, these deficits in health do not simply "add up". But since it is difficult to account for all of the complex interactions that occur between variables in the real world, some simplification is needed to make modeling possible.

### Bayesian Models

The essence of a Bayesian model is that it provides a formal way for updating current beliefs (the prior) when observed data lead to a new set of beliefs (the posterior). The Bayesian paradigm is well-established in the setting of diagnostic testing, where pre-test probabilities are converted to post-test probabilities based on new data (observed outcomes of diagnostic tests). For example, Sharieff and Tevaarwerk found similar results for the positive predictive value (PPV) of alpha feto-protein in diagnosis of hepatoma in Saudi Arabia whether they calculated PPV from their own data or applied Bayes' theorem to their prior belief to extrapolate evidence from a study conducted in the United States.[29] Bayesian models extend this approach to estimate unknowns, such as intervention effects (e.g. relative risks and odds ratios), prevalence and regression model parameters, using simulation techniques. Observed outcomes of the interventions may be either discrete or continuous. Uncertainty around these estimates is quantified by computing 95% credible regions (CRs), which are analogous to 95% confidence intervals.

Consider the regression model ($y = \alpha + \beta\, x$) in the Bayesian paradigm. The model starts with an expression of what is believed about β, for example, before data on $x$ and $y$ are observed. This expression of belief is formalized as a prior distribution. If there is prior ignorance, the prior distribution for β might be expressed as a normal distribution with mean zero and standard deviation 50, which suggests that there is a 95% probability that β lies in the wide range of -98 to +98. This represents a weak prior (also called vague or non-informative prior). Strong prior belief that ß is near zero could be incorporated by decreasing the standard deviation to 0.5, which puts 95% probability in the smaller range of -0.98 to 0.98. Next, the information from the prior and from the pairs of observations $x$ and $y$ in the regression model are combined to compute the likely values of β. This produces a posterior distribution. Since it is a distribution, the posterior allows calculations such as the probability that the true value of ß is greater than zero, or a range which has a 95% probability of containing the true value of β. With a weak prior, most information in the posterior would come from the data on $x$ and $y$. These results would be similar to results from a classical regression model. With the strong prior, a greater amount of information would be derived from the prior. The results that are found could be different if new data were scant in relation to the strength of the prior.

Returning to the example from the section about simple models, suppose that before the OPALS study was done, there was a vague belief (positive or negative) in the effectiveness of the AED program. In a Bayesian model, this belief would be represented by weak priors for ∂ and ß with normal distributions having means equal to 0 and standard deviations equal to 1000. Next, this belief would be combined with the observed data (183 out of 4690 patients survived before the AED program, and 85 out of 1641 patients survived after the AED program) to produce a posterior distribution. From the posterior distribution, it can be calculated that the OR is 1.35 (95% CR = 1.03, 1.74) which corresponds to 90 (7, 179) lives saved. This in turn corresponds to mean costs of $2,282 per life saved ($1,295, $15,300), and $133 per QALY gained ($66, $1394). In addition, the probability the AED program would be effective (i.e. lives saved > 0) would be 98%.

Now suppose that in another setting similar to Ontario (total population = 10 million), it is strongly believed that a similar effect would be observed after implementation of the AED program; in other words, the OR would be 1.33 (ß = 0.29). Data could be collected on 200 patients. Assume that out of these 200 patients, 100 had cardiac arrest before the implementation of AED program, of which 5 survived, and 100 had cardiac arrest after the program, of which 6 survived. Using the previous Bayesian model, the weak prior for can be replaced with a strong prior (mean = 0.29, standard deviation = 0.5), and data from the OPALS study can be replaced with the current data, producing a posterior distribution. From this posterior distribution, it can be calculated that the OR is 1.48 (0.4, 4.0) which corresponds to 107 (-469, 704) lives saved. This in turn corresponds to mean costs of $779 per life saved (-$11,240, $11,070) and $48 per QALY gained (-$863, $911). The probability that the AED program would be effective (lives saved > 0) would be 64%.

When more data are collected, the belief can be updated. Also, by using some cut off level for ICER (e.g. a cost of less than $50,000 per QALY gained), the probability that the AED program would be cost-effective could be calculated. Thus, the Bayesian approach can help in evidence-based decision making for resource allocation.

The advantages of a Bayesian approach are that information from other studies can be borrowed, prediction about future trials can be made, and inference regarding non-standard functions of the parameters is quite simple.[30,31,32,33,34] However, some level of training is required to carry out the technical aspects of model fitting and checking.

In summary, Bayesian models have a wide range of applica-

tion. However, each type of model has its own objectives and associated advantages and disadvantages (Table 1). To maximize advantages and minimize disadvantages for a given application, one might consider using a hybrid approach by combining elements of smaller, well-understood models that are more appropriate for particular components of the system being modeled. In order to use a computer model in the place of randomized clinical trials (RCTs), Sharieff *et al.* used a hybrid approach and simulated the physiology of iron absorption and regulation based on observations from two RCTs in which an iron supplement was given to Ghanaian children.[35] When baseline mean hemoglobin of Chinese children was fed into the model, the model accurately produced hemoglobin concentrations for that population in a third RCT. This model was extended to include the effect of zinc on diarrhea, the effect of diarrhea on mortality, the effect of hemoglobin on IQ in the surviving children and the effect of IQ on lifetime earnings. This was to estimate the cost benefit of a nutritional supplement containing iron and zinc, which would likely have some effects that persist over the entire lifetime. Thus, a very complex model can be built on several simple model 'blocks'. It is recommended that several models be considered for any particular question and, when a single type of model is not adequate, a hybrid approach be used.

| Model | Advantages | Disadvantages |
|---|---|---|
| Simple mathematical | Transparent | Not useful for complex problems |
| Complex mathematical | Useful for complex problems | Not transparent |
| Regression | Easy to build | May not be clinically relevant |
| Decision tree | Weighs benefit versus harm | May overestimate effects |
| Bayesian | Combines beliefs with data | No additional benefit in the absence of datences |

**Table 1.** Summary of Models

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# Decision-Making Errors in Medicine

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**Abstract**

In medicine, few would argue that decision-making is a physician's most common task, and often their greatest challenge. It is also the aspect of medicine that poses the greatest risk to patients. Arriving at a correct decision is the result of a complex mental process that depends on much more than simply knowing medical facts. Decisions can be strongly and easily influenced, for better or for worse, by a number of hidden assumptions and biases that the environment, a patient, a colleague, previous experiences and our perceptions impose upon us in any given situation. Like the art of taking an unbiased patient history, the art of decision-making must be learned and practiced. Unfortunately, most medical training programs do not include the study of decision-making processes in their curriculum, leaving their students to learn about these biases from their mistakes. It would be beneficial for professional schools to educate their students about the most common decision-making errors and to provide strategies to protect against their occurrence. This paper introduces some of the most common decision-making errors and biases, including confusion of the inverse, anchoring, the framing effect, the status quo bias, and several useful but risky heuristics.

## Decision-making Errors Every Doctor Must Avoid

In medicine, few would argue that decision-making is our most common task, and often our greatest challenge. It is also the part of our job that poses the greatest risk to our patients. Frequently, decisions must be made and acted upon in the face of an ambiguous patient history, a plethora of non-specific physical findings and incomplete test results. Medical school has changed significantly over the past two decades. Although medical students are still expected to digest volumes of medical facts (the so-called science of medicine), a greater emphasis has been placed on enhancing the doctor-patient relationship and developing excellent communication skills (the so-called art of medicine). These skills have evolved from being considered a luxury that some lucky patients found in their physician, to being essential, fundamental attributes expected from every practicing physician. Consequently, a strong emphasis on the development of interpersonal skills is an integral component of every modern medical training program. During these sessions, students are taught how to break bad news, obtain informed consent, and deal with angry or confrontational patients. Since empathy and compassion are important for proper patient care, most programs teach their medical students to be aware of the various ways in which their behaviour influences the thoughts, attitude and behaviour of their patients. Unfortunately, most training programs neglect the other side of the coin and fail to emphasize how, beyond simple stereotyping, the thoughts, judgements and decisions of physicians can be influenced by their environment, including stress, sleep deprivation, uncertainty, the way information is presented, and the behaviours of the patients themselves.

Physicians have to deal with the extremely demanding and competitive road through medical school and residency. Unfortunately, our education, combined with the nature of our profession makes us very susceptible to many avoidable decision-making errors. When I speak of "decision-making errors", I do not mean specific errors such as starting the incorrect antibiotic or using the incorrect dose. Rather, I am referring to errors and biases that affect the decision-making process and can ultimately lead to inaccurate judgments and decisions. The errors and biases that will be discussed are interrelated and rarely occur in isolation from one another. The process of decision-making can be divided into two broad phases, i) generating a list of alternatives, such as diagnoses or courses of action, and ii) choosing from among the alternatives. Decision-making errors are the result of biases and assumptions that either prevent us from considering or exploring possible alternatives or from properly choosing among them. Furthermore, many of these biases occur because of a misperception of probabilities. Let me illustrate with an example given by Scott Plous'[1] in The Psychology of Judgement and Decision Making. Suppose that you are a family physician and that, in your experience, only 1% of breast lumps you palpate turn out to be malignant. Now suppose that you palpate a breast lump that feels benign, but decide to refer your anxious patient for mammography just to make sure. Mammography has a sensitivity of 80% and, unfortunately the radiologist states that the lesion appears malignant. The following week the woman returns to your office and you inform her of the mammogram result. Her eyes fill with tears as she asks you "Are you saying that I have breast cancer?" Given these results, what is the probability that this lump is malignant? Before reading ahead, seriously think about what you would tell this woman.

If you are like 95% of physicians, you estimated a probability of malignancy between 75% and 100%. Sadly, you would be providing your patient with incorrect information and unnecessarily adding to her grief. The correct probability is around 7%. This very common mistake is called *confusion of*

*the inverse*. The sensitivity of a test tells us the probability of the test being positive for a patient who is known to have the disease. The mistake occurs when physicians believe the inverse has the same probability; in this case, the probability that the person has the disease given a positive test result. Although they sound similar, they are two different events with two very different probabilities. Although this error is not limited to physicians, making this or similar errors in medical diagnosis is of great significance and can truly place patients at risk. Despite the existence of a statistical formula which will provide you with the correct probability when faced with situations like the one described above, paying close attention to the initial probability of the event (the base-rate) and making small adjustments to it as new but imperfect information arises is the safest strategy. Often, the true probability of a particular diagnosis is close to what it was *before* the test was ordered. A test should be used to confirm what we already suspect to be true. With time, residents eventually learn about base-rate neglect. Most attending physicians try to emphasize the importance of considering the prevalence and incidence of various diseases when determining a working diagnosis for patients in the ER. However, formal education with respect to judgment and decision-making errors at an earlier stage would be beneficial.

Unlike the example above, most of the biases encountered cannot be clarified with the help of mathematics. Many biases operate subconsciously, concealing their presence deep within our final decision. The first two principles I learned while attending business school in Toronto relate to cognitive psychology and decision making. The first principle states that the brain often does not see what is right in front of it. The second principle states that the brain often sees what doesn't really exist. These principles arise from errors in basic perception and attribution. Perception is the subconscious act of giving meaning to what we see, hear and feel. The way we perceive a person or object relies heavily on our experience. Our brain likes to categorize events. When a new stimulus is encountered, such as a patient in the ER, our brain receives environmental cues, mainly visual, and cross-references these cues with a library of categories created throughout our life. When familiar cues are encountered, the target is categorized accordingly. For instance, one may categorize an individual as a 'drug-seeker' solely based on appearance, chief complaint and speech patterns. Categorization usually occurs within the first few minutes after the initial encounter and is extremely difficult to change, hence the importance we place on 'first impressions.'

The difficulty in changing a person's categorization results from our brain's dislike of inconsistencies. Once our target is categorized, our brain engages in *cue selectivity* which perpetuates a *confirmation bias*. This simply means that our brain ignores cues that conflict with our initial categorization, and attentively seeks cues that confirm it. Therefore, once this patient is classified as a drug-seeker, the doctor's behaviour and decisions, such as the decision not to perform elective surgery on this patient, or the decision to not order a CT scan to investigate the man's back pain, may be biased for the duration of the relationship. Interestingly, each one of us bases our perception on different central traits. Some of us may prioritize categorization by appearances while others may prioritize by speech and vocabulary. This can lead to differences in the way we perceive one another or our patients. Placing great importance on certain specific features when categorizing individuals also biases our decision-making when completing evaluation forms. For instance, if politeness is very important to you, then you may tend to evaluate a polite medical student, resident or attending supervisor very favourably in all domains, even if their surgical or teaching skills are below average. The opposite is also true. If someone values punctuality, then an individual who is chronically late may be rated poorly in all domains, not only in professionalism. The tendency of one important, central trait to influence the perception of other unrelated traits is called the *halo effect* and is a frequently-encountered problem in the performance evaluations commonly utilized in medical training programs.

Many of the common errors of judgement and decision-making result from the use of heuristics. Heuristics are 'rules of thumb' that we employ to simplify the decision-making process. Most of the time, heuristics are correct. However, if incorrect, the bias introduced will have profound effects on all future decisions. A heuristic that is related to the halo effect is the *representativeness heuristic*. In 1974 Tversky and Kahneman[2] found that people often judge probabilities based on the degree that A resembles a known population B. For example, one might be more inclined to suspect a young man with multiple tattoos to be an alcoholic rather than a confused 76 year old woman wearing her Sunday best. The image of a well-dressed, fragile, little old lady contrasts so strongly with our mental model of an alcoholic that we often fail to even consider the possibility. The same situation arises with men and osteoporosis.

Medical students early in their clerkship tend to perform a thorough history, and a complete head to toe physical examination. All pertinent positives and negatives are recorded and an attempt is made to make sense of the findings. Clerkship is a constant journey towards being comfortable enough to know how and when to perform a focussed history and physical examination. However, the more 'focussed' one gets, the more one relies on various heuristics when deciding what to focus on. I have seen several elderly patients who have been discharged home with 'normal' x-rays after a fall, only to return a week later with persistent hip pain and an inability to walk. Review of the initial pelvis x-ray usually reveals a minimally displaced pubic ramus fracture that was visible to the physician, but remained unperceived. This oversight does not necessarily imply negligence or a lack of focus. Rather, missed diagnoses such as this often arise when our brain is too focussed and fails to consider alternative diagnoses. This pubic ramus fracture was missed because the physician's brain had already categorized this patient as a case of an "elderly man post-fall; rule out hip fracture". When no hip fracture was found, the brain stopped looking for anything else. Heuristics can be helpful, but they should not be used unchallenged. When a situation appears atypical or confusing, identifying and testing the assumptions underlying your decision-making process may open your mind to new alternatives.

One might argue that these biases can be easily dealt with by involving a second party in the decision-making process. Unfortunately, this does not necessarily offer additional protection and can introduce a new set of potential biases. One

of the most influential of these is the *framing effect*. As I have discussed so far, every decision is made in a specific context or *frame*. Like artwork, we only pay attention to what is presented to us within the confines of the picture frame. The nature of that context can be a strong determinant of the resulting decision. Many events have their own natural frame. For example, when someone says they pay $1200 rent for a downtown condominium, everyone understands that this is a monthly rate. Changing the frame around a situation will change the way people approach the situation as well as the type of information to which they will pay attention. If someone is asked to select two objects out of a set of four, the individual will look for reasons to select two items over the others. If that same individual is asked to eliminate two of the items, that individual will seek reasons to eliminate two items over the others. Most decisions carry both benefits and risks. Framing a decision as a process of selection rather than a process of elimination changes the decision-maker's focus from the risks to the benefits of each alternative. If attempting to select the best antibiotic for a particular infection, the physician will tend to compare the benefits of each alternative, such as a simple dosing schedule and appropriate breadth of microbial coverage. On the other hand, if attempting to exclude antibiotic alternatives, the physician will tend to base the decision on a comparison of the risks or disadvantages of each, such as the cost, available route of administration or a salient side-effect. This is quite important since each decision-making process may lead to a different conclusion depending on which features were given the greatest importance. We not only impose our own frames on situations, but also are susceptible to the decision-making frames subconsciously imposed on us by others. For instance, if a patient is referred to the Pain Service "for treatment of unrelenting leg pain due to hip and knee arthritis", the Pain Service will likely initiate treatment based on the given history, when in fact the pain may be neuropathic in nature and require a different medication. In this case, the referring physician framed the issue as an arthritis problem and closed the consultant's mind to the possibility of an alternative diagnosis. Perhaps simply referring the patient for "unrelenting leg pain" may not have introduced that framing bias.

A very powerful bias that is frequently encountered in life and in medicine is the *anchoring effect with incomplete adjustment*. Anchoring is a heuristic that we use to simplify our decisions. When we make a decision based on ambiguous information, we subconsciously search for a reference point on which to base our decision and then make adjustments to account for some of the unique features of the current situation. Anchoring occurs when a certain piece of information, whether relevant or not, unduly influences our decision and prevents us from adjusting it appropriately. We become anchored very easily by almost anything. Retailers know and take advantage of this all the time. The MRSP or "manufacturers suggested retail price" listed on many price tags serves to anchor us on the high price, making the item seem more valuable than it really is. Therefore, we are more likely to purchase an item for $49.99 when the listed MSRP is $119.99 than if the item had no listed MSRP. In medicine, we can become anchored by the listed 'chief complaint' in a patient's chart just as easily as we can become anchored by numbers when making adjustments to a post-operative patient's analgesic dose. It is not difficult to see how a physician's approach to a patient with a stated complaint of 'lower back pain' would be different from their approach to a patient complaining of 'flank pain', even though both may be due to renal problems. All other information gathered during the focussed history and physical examination will be interpreted in the context of the stated chief complaint, thereby influencing the physician to over-emphasize findings that support the common diagnosis of 'muscular lower back pain' and under-value the importance of new information that may point to the true diagnosis, such as assciated groin pain. Once anchored to a diagnosis, only very compelling evidence will change the physician's mind. This is why patients who have suffered from a missed or mis-diagnosis are so frustrated. They often challenged the diagnosis several times, provided the physician with new information and repeatedly emphasized that "something else is wrong" before the diagnosis and treatment plan were appropriately altered.

I have been providing examples with a focus on physicians, but resistance to change is a universal phenomenon known as the *status quo bias*. This bias is introduced into decision-making processes because people are generally reluctant to change the current course of action, or default decision. The status quo bias is so powerful that it can influence the actions of entire nations. For example, in Canada, the rate of organ donation is a mere 18%. However, in some Scandinavian countries the donation rate is over 60%. Why the difference? Well, the main difference is the status quo of these countries. In Canada, the legal status quo is that individuals are not organ donors unless informed consent is obtained from the individual ahead of time, or from their family. In other words, to donate your organs, action must be taken. In contrast, in countries with higher donation rates, presumed consent applies to organ donors. That is, every eligible person is presumed to be an organ donor unless the individual or their family sign forms against it. In this situation, action is required to *not* be a donor. Therefore, the main difference in organ transplantation rates is due to people's reluctance to change the default option, whatever it may be. People are uncomfortable taking action to stop what will happen automatically. In fact, digressing from the topic of medicine, this strategy is being employed with increasing frequency by various companies who offer to provide you with a service (say, three extra high definition movie channels) free for the first three months, but $22.50 per month thereafter unless you download, complete and mail-in a service cancellation form. The companies know that people do not like to take action in order to stop something that is already in progress. Furthermore, these companies are preying on our natural aversion to losses. Once we get accustomed to having the new HDTV movie channels (that we were living perfectly well without prior to their phone call) we will experience a significant loss when we lose them, hence prompting us to continue paying for the service.

Loss aversion causes people to over-estimate real or potential losses and under-estimate real or potential gains. This can affect the decision-making processes of physicians and patients alike. For patients, loss aversion is often manifested during the process of obtaining informed consent. In general,

one larger loss is easier to handle than multiple small losses. As a result, quoting a total complication rate of 6% is much less distressing to patients than listing twelve separate possible complications with a probability of 0.5% each. As a result, one strategy to reduce the loss aversion felt by patients is to "lump" all complications together and provide one overall complication rate, and then, describe each possible complications without attaching a specific probability to it. Additionally, it would be preferable to end the discussion with an emphasis on the benefits of the proposed treatment.

Physicians frequently manifest loss aversion as well. Anyone who has used the phrase "the enemy of *good* is *better*" is really uttering a caution against the effects of loss aversion. Loss aversion is the fuel that feeds the surgeon's struggle to improve the fracture reduction by just one millimetre, even though the improvement is unlikely to impact the outcome of the patient. Loss-aversion often leads to short-sightedness, which biases our judgment by placing excessive emphasis on the present and ignoring the future. This is not an argument in favour of mediocrity and complacency. I strongly encourage the pursuit of perfection and follow the wisdom of Dr. Robert B. Salter who said "trifles make perfection, but perfection is no trifle." My only caution is to be aware of the effects of loss aversion and myopia and to take measures to ensure that the pursuit of perfection is not compromising the outcome rather than improving it.

The endeavour of this paper was to raise awareness regarding the many judgement and decision-making errors to which we as humans and knowledgeable professionals are very susceptible. Awareness is the first step in protecting oneself and one's patients from the potentially harmful consequences that can arise from the hidden influence of these biases and heuristics. They will be experienced by every physician, who, with time will learn about their characteristics, power and consequences and strive to avoid them. Perhaps exposing medical students to these common influences early in their training will provide them with the knowledge necessary to protect themselves, without having to learn from their mistakes in clinical practice. The medical field is in constant, rapid evolution. Students should not focus on memorizing which decision to make in every circumstance, because that constantly changes. Students need to learn the process that will lead them to the right decision, because that will never change.

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# The HPV Vaccine: Ongoing Ethical and Policy Issues

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Cervical cancer kills 370 women a year in Canada.[1] These deaths occur despite national efforts to screen all women with Papanicolaou (Pap) smears. Cervical cancer mortality is largely preventable when dysplastic lesions are detected early. However, a recent national survey indicated that, between 2000 and 2003, 27.2% of women aged 18 to 69 years were not screened with Pap testing.[2] Similar levels of complacency exist in countries outside Canada. The UK recently reported that 30% of women between the ages of 25 and 29 were not being appropriately screened.[3] While cervical cancer screening programs have drastically reduced the number of cases, the prevalence of cervical cancer indicates that the disease has not been eliminated.

In the March 2007 edition of the *UTMJ*, Michelle Levy reviewed the safety and efficacy data of Gardasil, the HPV vaccine developed by Merck and approved for public use by Health Canada on July 18, 2006.[4] Gardasil provides persistent protection against the high-risk HPV subtypes 16 and 18 for up to three years.[5] HPV 16 and 18 cause 70% of all cervical cancers. Gardasil also protects against HPV subtypes 6 and 11, which are the pathogens responsible for 90% of all genital wart infections. GlaxoSmithKline is also developing an HPV vaccine called Cervarix, which is currently in phase III clinical trials. Clinical trials sponsored by Merck and GlaxoSmithKline indicate that there are no safety concerns with the administration of either of the HPV vaccines.[5,6] Available data suggests that the HPV vaccination is both safe and effective.[5,6,7] Despite the early success of Gardasil and Cervarix clinical trials, there is considerable debate amongst the general public and the medical community concerning how, and to whom, the vaccine should be delivered. In spite of this debate, the HPV vaccine has progressed from clinical trials, to regulatory approval, and to a publicly delivered vaccine at an extraordinary rate. In the Fall of 2007, the provincial governments of Newfoundland and Labrador, Prince Edward Island, Nova Scotia, and Ontario will begin providing the vaccine in schools in publicly funded programs.

Discussions about the HPV vaccination can be polarizing, especially for parents. After all, the vaccine is currently approved for young girls to prevent a sexually transmitted virus. This article will examine some of the ethical and political issues surrounding the HPV vaccination. In addition, recent legislation outside of Canada that makes the HPV vaccination mandatory will be discussed. Finally, the challenge of delivering the HPV vaccine effectively to women in the developing world will be explored.

## The Debate Continues - Ethical and Political Issues surrounding the HPV Vaccine

The goal of HPV vaccination is to achieve lasting immunogenicity against high-risk HPV subtypes before young women become sexually active and exposed to the virus. Gardasil approval in Canada is for girls 9 to 26 years of age. Vaccination in countries mandating HPV vaccination is recommended at age 11 to 12 years, before most girls have reached menarche. A vaccine for a sexually transmitted disease for children raises a number of issues. Many faith-based groups and religious conservatives have vociferously opposed the vaccine, believing that a vaccination for a sexually transmitted infection sends the message that sexual activity is safe, and that the HPV vaccine may promote sexual activity in adolescents and weaken abstinence-based programs. Yet, not all faith-based advocacy groups are unequivocally opposed to the vaccine. Focus on the Family, a charitable Christian organization in the U.S. and Canada, is opposed to mandatory vaccination but supports vaccine use on a voluntary basis.[8]

One difference between HPV infection and other infections that are routinely immunized against, such as diphtheria and measles, is the role that behaviour plays in infection. Measles is a respiratory disease spread by aerosol transmission from patient-to-patient. There is no behaviour that an unvaccinated person can engage in to ensure they will not contract the measles virus if an infected individual coughs on them. Conversely, as a sexually transmitted disease, there is a behavioural or lifestyle component associated with the acquisition of HPV.[9] Individuals who are sexually active are at high-risk of a HPV infection, while those who abstain from sexual intercourse are not. Among at risk individuals, HPV infection is pervasive. Up to 39% of female university students are infected with a subtype of the HPV virus 24 months after becoming sexually active.[10]

Gardasil is not the first vaccine for an infection that is sexually transmitted. Canadian children receive routine vaccination for hepatitis B, another infection that is transmitted mainly by sexual contact. Those supporting abstinence programs feel the HPV vaccination may be harmful to their message even though there has been no evidence that mandatory vaccination against hepatitis B has negatively influenced safe sex practices, or the rate of sexual activity among adolescents.

Another debated issue is whether young boys should receive the HPV vaccination as well as young girls. Modeling studies demonstrate that a female-alone vaccination approach would only be 60-75% as effective at reducing HPV prevalence in women as a vaccination strategy that targeted both sexes.[11] One reason for this theoretical increased effectiveness when targeting both sexes is an increase in 'herd-immunity'. In theory, any strategy attempting to deliver the HPV vaccination to large segments of the population would be strengthened by the vaccination of boys as well as girls.

In an attempt to determine whether it is ethically appropriate to mandate the HPV vaccination, the potential harms and benefits must be considered. The benefits include a reduction

in the prevalence of HPV infection, genital warts, and cervical cancer. Potential harms include: (i) a potential contribution to complacency towards safe sex practices, (ii) rare adverse reactions to the vaccine that are not yet known, (iii) the infringement on a parent's right to decide what is best for their children if vaccination is made mandatory, (iv) the possibility of a shift in the HPV subtypes that cause cervical cancer to modify away from those subtypes contained in the vaccine and (v) the risk that HPV vaccination might have a deleterious effect on existing Pap smear screening programs. A recent article in which an ethicist used a utilitarianism approach (where the consequences of a decision determine its ultimate worth) to evaluate HPV policy options concluded that the mandatory universal vaccination of all children at age 11-12 years is ethical and appropriate.[9] The decision, however, is ultimately a personal one that must be made by patients and their families.

## Full speed ahead – publicly funded HPV vaccination programs

In September 2006, the Michigan Senate enacted a bill legislating the mandatory immunization of all girls aged 11-12 with Gardasil. Many American states followed this lead; currently 23 states have tabled legislation that mandates HPV vaccination for all public-school aged girls.[12] The legislation is controversial and at least two states have withdrawn bills, while many others are actively debating the issue. Texas governor Rick Perry faced intense criticism when it was discovered that Merck made donations to his election campaign, after which he initiated legislation mandating Gardasil vaccination. In other countries, Britain's Joint Committee on Vaccination and Immunization has yet to decide whether Gardasil will be publicly funded. Australia is adding Gardasil to the list of publicly funded vaccines and will be providing it for both men and women.

In Canada, the federal budget of the Conservative government was released in March 2007 and has allotted $300 million over 3 years for provinces and territories to provide Gardasil to Canadian women and girls.[13] Many provinces have clamoured to begin school-based vaccination with the allocated funds. The four provinces noted above will begin programs this Fall, while British Columbia is slated to begin in the Fall of 2008. It appears as though the usually slow pace of scientific debate has been rapidly outpaced by these policy initiatives. Any harboured misgivings about broad HPV vaccination programs will soon be put to the test.

Despite the heated public and political debate, driven by the initiation of publicly funded vaccination programs, support for the HPV vaccination in the scientific literature is strong. Editorials and reviews in Canada, the United States,


**Figure 1.** HPV Vaccination Program by Province and Territory

and Britain acknowledge the tremendous public health potential of the vaccine to decrease cervical cancer mortality globally.[1,11,14,15] Editors for The Lancet support the mandatory vaccination of all girls aged 11-12 years in the European Union.[11] However, a response from a Public Health Lead for cervical cancer screening in Britain cautions that, in countries with effective screening programs, a rush to mandatory vaccination "will worsen, HPV-related illness by undermining existing screening and leaving women less protected than now".[16] Similar concerns exist in Canada as well.

Canadian organizations with expertise in immunization and women's health have also embraced the new vaccine's potential. They, however, remain ambiguous on the role of mandatory HPV vaccination in Canada. Health Canada and the National Advisory Committee on Immunization encourage the use of the HPV vaccination, but do not provide a clear recommendation as to whether the vaccine should be mandatory.[17] The Society of Obstetricians and Gynaecologists of Canada applauds the recent funding allocated for HPV vaccination by the Conservative government but also does not clearly comment on the role of mandatory vaccination in this country.[13]

## Where it is needed most - delivering the vaccine to developing countries

The disease burden of cervical cancer in Canada and other Western nations pales in comparison to that in developing countries. It is estimated that there are 500,000 new cases of cervical cancer globally, resulting in 240,000 deaths.[1] Cervical cancer is the second leading cause of cancer deaths among women worldwide. The majority of these deaths occur in countries without effective screening programs in place. Poverty is a major reason for inefficient or absent cervical cancer screening in these countries. This is also a reason why individual women may not be able to afford the $400 US required to purchase Gardasil to vaccinate themselves or their children.

Organizations such as PATH (Program for Appropriate Technology in Health), a non-profit group that attempts to improve global health, see great promise in the HPV vaccine. PATH is collaborating with the World Health Organization and The Bill and Melinda Gates Foundation to deliver the vaccine, in an efficient and affordable way, to women in developing countries.[18] Delivery of the HPV vaccine to developing countries is a massive undertaking but in the end, the global success of Gardasil and other HPV vaccines in reducing cervical cancer deaths will depend on how efficiently they are delivered to women in the developing world.

## Conclusion

The development of a vaccine targeting the HPV virus holds great potential for decreasing deaths due to cervical cancer worldwide. Controversy continues about what constitutes an ethical and just vaccination policy. The numerous interest groups involved – pharmaceutical companies, faith-based groups, governments, physicians, and parents – produce an interesting debate. Many issues remain unresolved. For example, data does not exist on the long-term efficacy of the HPV vaccine. It is unclear when and how often booster shots will be required. Also, a coherent strategy will be needed to ensure that women who receive the vaccine will continue to be screened with Pap testing.

Many uncertainties remain, but the vaccination of girls in Ontario schools will begin in Fall 2007. These vaccination programs will surely result in a flood of questions from concerned patients and their parents in the offices of their family doctors. Effective public policy at home and public health initiatives abroad will determine whether the potential of the HPV vaccination to reduce cervical cancer mortality will be realized. Canadian physicians must be able to accurately describe the science surrounding the HPV vaccine and cervical cancer, as well as the risks and benefits of the vaccine, in order to counsel patients and participate in the public debate.

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# Current Topics in Postgraduate Medical Education: An Interview with Dr. Sarita Verma

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The Canadian Resident Matching Service (CaRMS) is a national not-for-profit organization that provides electronic application service and a computer match for Canadian and international medical graduates applying for a residency position. CaRMS is currently chaired by Dr. Sarita Verma, LLB, MD, CCFP, FCFP. She is also the Vice-Dean of Postgraduate Education within the Faculty of Medicine at the University of Toronto. With the majority of medical students unaware of the process and issues surrounding CaRMS, we decided to interview Dr. Verma to discuss the issues that are at the forefront of students' and residents' minds and to learn more about her career and role within the faculty.

**Can you describe the academic and career path that led you to where you are today?**

My first professional degree was in law at the University of Ottawa. I articled in Ottawa and then joined the Foreign Service. In my first year there I wrote the BAR exam in Ontario. I worked at the Department of External Affairs as a Foreign Service Officer and seconded to the UN and was posted in Sudan and Ethiopia. After that, I went to McMaster Medical School. I did my residency at Queen's University in Family Medicine, completed a third year in Care in the Elderly from which I graduated in 1994, and became a Postgraduate Dean at Queen's in 1998. I became Associate Dean in Medical Education at Queen's in 2003 and then left Queen's in 2005 and came to the University of Toronto as Postgraduate Dean. So I'm a family doctor and a lawyer.

**It seems like you advanced very quickly in your roles. Did your legal background help?**

Yes. Although I do not formally practice law anymore, I think I am the only doctor-lawyer in the post-graduate world. Within academic administration, one of the reasons why I became an associate dean in 4 years was because 80% of my work involves some form of administrative law and much of it involves employment law, dispute resolution, and some litigation. Much of what I do now involves helping the medical school deal with legal issues. I would say that it is unique.

**As a doctor, lawyer, and administrator, how is your career divided amongst the three?**

I probably practice more law than medicine right now. I had previously practiced about 50% clinical medicine until I moved here (Toronto) and this is such a big enterprise that really, I am probably at around 90% administrative/policy with between a half-day to one full day of clinical medicine a week.

**One day a week doesn't seem like a lot of time. Do you find that to be enough?**

I would like to be more clinical, but it is not feasible in this job. I have colleagues who stopped practicing medicine because they took on decanal or senior administrative roles. 'If you don't use it, you lose it.' Your real reason for existence is being a doctor and I think that a lot of people forget that. I like being a family doctor. It is a very fun thing to do and very satisfying.

**Apart from your role within the university, what are some of your other roles in external organizations?**

A big part of what happens when you are in these types of jobs is that you are placed into committees, and you can be a committee member who goes to meetings and eats their lunch and leaves, or you can be like me and say, "If I'm here, I'm going to make a difference. I'm going to do something". I am on Toronto-based committees, provincial committees, and national committees. One of the things I enjoy most – and I am in the last year of it – is my role as Chairperson on the Board of CaRMS. I have also been on a number of Royal College (of Physicians and Surgeons of Canada) committees. I do some health human resource work on provincial and national committees. I think that sort of leadership is really important. Being one of the few family doctors who are in that context, it has really made a difference to be in a room full of specialists and to be able to speak for Family Medicine.

**Can you elaborate on your role within CaRMS?**

CaRMS is the Canadian Resident Matching Service and it is about 25 years old in its current incarnation, although the whole system has been around for much longer. In the last fifteen years, it has really developed a governance structure where there is a board of directors who come from memberships, such as the CFMS (Canadian Federation of Medical Students), AFMC (Association of Faculties of Medicine of Canada), Royal College of Physicians and Surgeons of Canada, CMA (Canadian Medical Association), Federation of Medical Regulatory Authorities of Canada, CAIR, (Canadian Association of Internes and Residents), the Association of Canadian Academic Healthcare Organizations, and the College of Family Physicians of Canada.

As the Chair of the Board, the 'governance' part of it is actually hearing from the management, which is run by an

executive director, CEO, and a staff of almost twenty people. The Board meets twice a year, at which time we hear what the systemic issues are, and then set policy. Policy never comes to CaRMS unless an issue arises from management.

*What are some current policy issues with CaRMS?*

One of the policies that I wrote and was very involved in during the last two years was called the Match Violations Policy. What we heard consistently after the match, or during the match, was that there were some programs that placed pressure on students to tell them how they were going to be ranked; a lot of what I would call "unprofessional behaviour." We also learned that some students felt that some of the interview questions were inappropriate and may not have followed appropriate protocols for employment. Some programs might have contacted students who had already matched elsewhere and said, "We'll have an open vacancy, come to us, it would be a good contract", or students who got in somewhere but discovered an open vacancy somewhere else decided to try for that position because that is where they really want to be. Those are all match violations and we had previously lacked a process to deal with them.

The other policy that we put into place was integrating non-Canadian medical graduates (International Medical Graduates, IMGs) into the match. So how does something like that happen? Well, CaRMS is a service organization that runs a match; it is very much like a booking service. Policy changes started with the Ministry of Health who said, "We want to increase the capacity of training physicians in Canada and we want to allow IMGs into the match."

That had a domino effect, which reached the medical schools and they decided to allow IMGs. Who implements that change? It is CaRMS. So CaRMS must establish a mechanism that ensures people can apply and be matched. An important point to remember, however, is that we do not actually set the policy. Our policies are really governance policy, like deadlines and timetable policies, for example.

**There has been a lot of concern from students with respect to the inclusion of IMGs. What is the situation in Ontario now and what will it look like down the road?**

Ontario still has a parallel stream for IMGs this year, but IMGs will be merged into the second iteration of the match next year. Starting in July 2008 (which is the match for residents starting in July 2009) there will be a merged match. So, for the first round, there will still be two separate streams, but for anything left over in the second round, Canadian Medical Graduates (CMGs) will have to compete with everyone, including IMGs. The good news is that there are enough positions in the match. There are more positions in the match than CMGs needs to worry about. Also, history shows that our CMGs are extremely competitive and that they will not go unmatched unless they have a poor academic record or they have chosen positions with very few PGY1 spots. Not everybody is going to get into highly competitive spots, such as plastic surgery, so those who do not get into plastics will have an alternate career. But if you are a good clerk, have a good academic record, and are applying competitively, you will have no trouble at all. There are plenty of spots. So let us not be driven by the usual 3 to 5 people who do not get matched because, to be really honest, it is possible that they are not competitive anyway.

**In the last CaRMS cycle, there were some UofT students that were unmatched in the first round. Were they matched in the second round?**

I think so. Some people do not go into the second round because they go to the United States, take a year off, finish off their PhD, or engage in research. To my knowledge, everybody got matched. All positions at the University of Toronto were filled in the first round. Consistently, 96% of UofT students get their first choice of discipline within their top 3 choices, 86% get their top choice, and about 60% get their top discipline and location. So, I think it is a very successful match.

**The whole CaRMS process can be quite stressful. Do you have any advice or recommendations?**

For those that are currently preparing their application, there are three things that influence the application. First is your academic performance. If you have been doing well, Bs or passes – I am not talking about honours – you will get matched. If you have a spotty record, with some fails, you will have problems with the match because people will want to know what those fails were about. But, if you have had straight passes all along, you will get matched.

Second is your letters of reference. Letters have to be from people who know how you function clinically but not specialty specific. So, for example, if you are picking pathology, the reference does not have to be from pathology, but will have to be from someone who can attest to your clinical skills and knowledge in the field of pathology. Additionally, they have to be from someone who knows you and has observed you in a clinical setting. It needs to be from someone who you have spent time with in a clinical setting. In fact, it is not a bad idea to go for a reference from a junior faculty. Most students go after the "grand poobah" doctor, someone who they might not have worked with as closely. Finally, you will receive a lot of criticism during residency, but if you are defensive, arrogant, and cannot take it, those are the things we do not want.

Third is your interview – a 15-20 minute interview does not necessarily help you select a person, but it certainly does help you unselect a person. You can often predict some of the most common questions, such as "Why are you interested in this specialty?", "What have you done to find out about this specialty?", "What are your experiences in this specialty?", and "Tell me what you know about our school and what you know about our program". Additionally, be prepared to ask intelligent questions. Always do your homework and be professional.

Looking farther down the career path, there used to be some discussion around a new model of residency called the Core Competency Model. Has there been any progress? (For those unaware of this issue, this new model was a joint Royal College of Physicians and Surgeons of Canada and Canadian College of Family Physicians initiative. It was aimed at reducing the stress for early career decision-making by allowing students to choose a speciality or subspecialty at a later stage in training.)

The Core Competency Model is hard to implement. I have been involved in many discussions on this matter and the Royal College has been trying to find a way to pilot it. I do not see it as a threat looming in the immediate horizon (two-three years), but it is a notion that comes up every few years.

Many residents enjoyed the rotating internship (abandoned in the early 1990s) and many residents want to moonlight. From a system point of view, if you are going to be a cardiologist, then you are also a general internist. There is the desire to avoid having students become interventional cardiologists in their PGY1 year. A lot of people, however, do not practise general internal medicine and that is the problem. We still want them to practise the generalist skills. We are concerned that psychiatrists graduate and they do not know how to treat straightforward pneumonia. Instead, they refer to general internal medicine or to respirology. We are concerned that when a resident wants to switch programs, they have to start all over again and there is a lack of flexibility. So there are good reasons why one would want to have a core model and why one would want to have the opportunity for people to actually learn to be real generalist.

**You mentioned "moonlighting." The ability for residents to work extra shifts already exists in provinces like Alberta. Is it true that Ontario is going to try something similar?**

University of Toronto has approval, in principle, from the College of Physicians and Surgeons of Ontario (CPSO) to take that forward as a pilot project. The hope is that we will have a system in place that could be launched by October 15th, and that we will be accepting applications for moonlight activity that begins in January 2008.

The proposal that I put in was for two years plus an additional one year extension as an evaluation phase. This is an incredibly big change for Ontario. I became personally engaged to this issue when I came to Toronto for three reasons. One, was because the Ministry wanted this to be one of the solutions to the emergency room crises and to give residents a chance to address that.

Two, I believe residents actually should have graduated licensure. I think that it makes more sense for residents to have the opportunity to experience and model other office environments as they are training, and not just learn as part of their educational program. They will never learn those skills unless you go out and practice. They will have to learn how to manage call under different clinical environments, manage patients, take responsibility for them, look things up – it is very different when you are doing such things as a semi independent practitioner versus as a resident. And three, I think residents will acquire knowledge and skills in professionalism, management skills, communication, and collaboration that could not be learned in any other way.

**Under this system, who can apply for a restricted license?**

We have not figured that out yet because it is very limited. We are probably going to start with emergency and internal medicine. We may add on paediatrics and anaesthesia, and then gradually, will add other programs. It seems to be at the PGY3, 4, and 5 levels, but not before that because we still want experienced people taking care of others. Also, it would be in a supervised environment – the expectation from CPSO is that they will be working where they are competent and where they can be supervised.

**You are certainly involved in many aspects of postgraduate medicine and have done a lot to improve the system. With all that you do, what is the most rewarding part of your role?**

The work hours are sometimes very challenging, but the rewards are worth it because a lot of what I do influences public policy and helps to ensure social accountability. The best part about my job is actually working with students and different people from the various medical organizations. It is so much fun. Students are always creative and enthusiastic and they keep me enthusiastic about what I do. I would encapsulate that the best part of my job is being able to work with up-and-coming thinkers, and hopefully having an impact in what they do in the future.

**Do you have any final words of wisdom for students?**

One message I want to get through to students on the match is that I do not know of any University of Toronto students who have done badly. If they have done poorly, it is because they have not done their homework, they have performed poorly in their academics, or they become ill. Otherwise, it is very rare. The important thing to remember is that not everybody can get exactly what they want. There are a limited number of spots in some specialties.

The other thing is that when you have your summers when you are not in clinical activities, then take and enjoy your holidays. You do not need fifteen observerships. You just need to do really well in your clerkship rotations. People are looking for a well-rounded person; they are not looking for a brilliant jerk. They really like genuine people.

*We would like to thank Dr. Verma for taking the time to discuss the issues surrounding the residency matching service. Her knowledge and insight in the Canadian medical education has not only contributed to this article, but has also had a positive influence in the policy affecting our medical education.*

Nam Le and Kevin Koo served on the University of Toronto Medical Society. They have represented medical students on various local, provincial, and national level organizations such as the Ontario Medical Student Association (OMSA) and the Canadian Federation of Medical Students (CFMS), and have advocated on numerous platforms in issues surrounding medical education.

# CHIUS: Community Health Initiative by University Students

Andrew Thamboo (0T9), Co-Chair, CHIUS, University of British Columbia, Vancouver

Ensuring social accountability is an important mandate of all medical schools. While the current undergraduate curricula foster opportunities to promote such accountability, medical students, with the guidance of their faculty, have been equally proactive in creating other opportunities for their colleagues. The Community Affairs portfolio of the University of Toronto Medical Society, in collaboration with the Office of Health Professions Student Affairs, directs over twenty programs to help various community groups including seniors, single mothers, children from diverse backgrounds, and the homeless. Other medical schools, including the University of British Columbia and the University of Saskatchewan, have developed student-run, interdisciplinary health/wellness clinics to benefit local groups. The ensuing articles describe the programs, their history and structure, and the remarkable impact on the health of several individuals.

*– The Editors*

The Community Health Initiative by University Students (CHIUS) is an inter-professional, student-run, primary health care and health education program that operates in Vancouver's inner city. Founded by two University of British Columbia medical students, since its inception, CHIUS has rapidly evolved to include over 500 volunteer students who represent ten health-related faculties (Medicine, Nursing, Social work, Pharmacy, Physiotherapy, Occupational therapy, Dietetics, Dentistry, Audiology/Speech, and Health administration).

CHIUS volunteers provide inter-professional primary health care, along with referrals, to other community services and to the residents of the Downtown Eastside (DTES). This exposes students to the social issues of an under-serviced inner city environment, while improving the health of the community by adapting and sustaining this community health outreach program. Moreover, CHIUS has created educational modules from different health disciplinaries that are delivered by students and health care mentors to residents of the DTES.

CHIUS is unique in several ways. First, the students initiate the encounters with the patients, complete the medical assessments and propose the management plans. This work is supervised and reviewed by a physician. Second, the emphasis is not only on providing medical care, but also on health education, harm reduction, and promoting the social, emotional, and mental aspects of health. This includes several students in the reception area who provide community members with interactive, non-judgmental conversation. Finally, time is set aside at the end of each shift for a reflection session during which the health care team shares their experiences, discusses any concerns, and receives feedback from one other.

CHIUS has a level of inter-professional innovation unlike any other. The mission of CHIUS is to provide an exciting and innovative program that emphasizes the development of mental, emotional, social, and physical well-being of all participants in a safe and welcoming environment. Our inter-professional team strives towards diminishing barriers to health care, establishing strong partnerships, and enhancing the community's perception of health care. We also actively evaluate and refine our service to ensure the continuous delivery of a high quality program that is responsive to the needs of all participants.

CHIUS offers drop-in sessions and community outreach programs involving many, if not all, disciplines with follow-up reflective meetings. Since 2005, CHIUS has developed unique programs that focus on nutrition, prescriptions, foot care, diabetes prevention, dental care and screening, physiotherapy, first aid, heart health and blood pressure, and hypertension. There are several more programs currently being developed and due to the positive feedback that we have received regarding our programming events, we have expanded to the Vancouver Native Health Clinic in order to meet the needs of all marginalized individuals in the DTES.

CHIUS operates under a service learning model. Students from the various disciplines learn from and work along side each other through integrated clinical activities. This team approach is virtually unmatched in any student training setting, where primary care is provided through inter-professional teams of health science students followed by interdisciplinary student shadowing.

It is our vision that CHIUS will gain national recognition as a model for student driven health initiatives that respond to the needs of marginalized communities. Through partnerships, CHIUS aspires to facilitate the development of similar initiatives at all Canadian health sciences schools.

# SWITCH: Student Wellness Initiative Toward Community Health

Carole Courtney, SWITCH Coordinator, University of Saskatchewan, Saskatoon

On October 12, 2005, the Student Wellness Initiative Toward Community Health (SWITCH) opened its doors to clients and made history by becoming one of only three student managed inter-professional health care centres in Canada. Modelled after Vancouver's CHIUS, SWITCH has been providing after-hours inter-professional clinical, social, and program services from Westside Clinic and other locations as necessary to residents of Saskatoon's core neighbourhoods.

At any one time, almost 200 students in Medicine, Nursing, Social work, Clinical psychology, Physical therapy, Kinesiology, Pharmacy, Nutrition, Public health, Arts and Science, and Dentistry from the University of Saskatchewan, University of Regina, and Saskatchewan Institute of Applied Science and Technology work alongside professionals from those same disciplines and more. SWITCH's unique approach to health care makes it the most inter-professional primary health care agency in Saskatchewan.

With a yearly budget of just over $200,000, SWITCH employs a full time coordinator, a part time volunteer coordinator and a clinical staff consisting of a physician, nurse, receptionist and cultural support worker. Additionally, on each shift, there are 3-6 professional mentors and 5-15 student volunteers. SWITCH sees an average of 46 clients per three hour shift.

Using the Westside Clinic to deliver services, SWITCH extends the hours of available health care on Saskatoon's west side by operating two shifts per week year round. Shifts are currently Wednesdays from 5 p.m. – 9 p.m. and Saturdays 10:30 a.m. - 2:30 p.m., with plans to expand when Westside Clinic and SWITCH move to their new facility in Fall 2009.

While clinical services are important, SWITCH also develops and delivers its own programming. For example, each week includes a *Wednesday Women's Drop-In Night*, where women take part in a schedule of workshops, such as how to make handmade soap, basic sewing, beading, and others. Every other Saturday is *Children's Health Day* where the normal complement of students and professionals are augmented with paediatric personnel. The second Saturday of each month is the *SWITCH Dental Clinic* where dental professionals and students provide free basic dental services. In addition, SWITCH is in partnership with *Fitness-Food-Fun*, a very successful drop-in program for chronic disease management, and also with Saskatoon's Public Health and Community Addictions Services to link clients to services.

"It's a one-stop approach to health for Saskatoon residents and a creative approach to providing educational experiences for students. We're extremely grateful to our partners the Saskatoon Community Clinic, the University of Saskatchewan, and Saskatoon Health Region – Primary Health for taking this leap of faith with us." says SWITCH Coordinator, Carole Courtney.

As a non-profit registered charity, SWITCH does all of its own fundraising but receive funding and organizational support from its partners and other organizations. Awards won include Saskatoon's Award for the Elimination of Racism and the recent Tommy Douglas Excellence in Health Care Award. SWITCH hopes to pave the way to a better primary health care model and provide Saskatchewan with future health care professionals who are able to treat the whole person, and are sensitive to the needs of inner city people, especially those of the First Nations and Métis descent.

SWITCH provides a welcoming atmosphere for community residents. Arts and science students and those in the early years of their health science training make coffee and snacks, provide childcare for program participants, and provide a community centre atmosphere by talking with clients. Upper level students and mentors see clients for clinical and counselling services, while students of all levels will help with programs. At the end of each shift, all staff and volunteers sit down to reflect on their experiences, the challenges of working inter-professionally, how best to serve clients, and to determine aspects of the project on which to improve.

Recently, SWITCH was fortunate enough to be able to take part in a joint workshop offered by CHIUS as a part of the Canadian Association of Family Medicine Faculty conference in Victoria, British Columbia. At this workshop, representatives from all four Canadian student managed health care initiatives were able to trade information regarding their respective projects and talk with students from other universities about starting their own projects.

If you would like more information about SWITCH, go to www.SWITCH.usask.ca, email student_clinic@yahoo.ca or call 306-956-2518.

# Cranial Nerve Palsy: An Unusual Presentation of Metastatic Prostate Cancer

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Rodrigo Cavalcanti, MD, M.Sc., FRCPC, Faculty of Medicine, University of Toronto

A 79 year-old Italian man presents to the Emergency Department with a 4-month history of progressive dysphagia, dysarthria, left-sided hearing loss, diplopia and left facial droop. These symptoms have worsened significantly over the past month, limiting his oral intake to pureed foods and liquids. His speech has also become unintelligible. He denies any fevers, chills, or loss of appetite, but has had increasing fatigue. A review of systems is otherwise negative. Past medical history is significant for tinnitus, affecting his left ear for over 20 years, and occasional joint pain in the legs. There is no history of TB exposure and the patient immigrated to Canada 38 years ago. His medications include meclizine, for dizziness, and clonazepam for sleep.

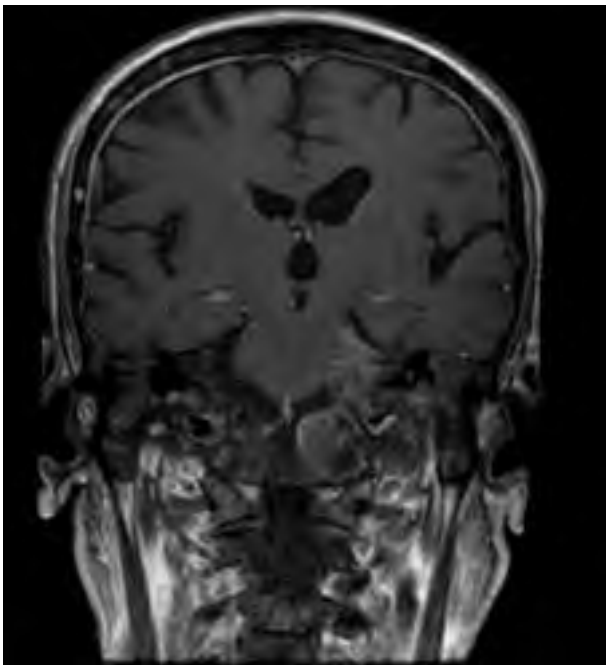
On examination, the patient is afebrile. Blood pressure, respiratory rate and oxygen saturation are normal. Heart rate is 110, regular and bounding. The head exam is significant for dry mucous membranes and dark pigmentations on the tongue. The cardiovascular, respiratory, and abdominal examinations are unremarkable. A detailed neurological examination reveals intact mental status and normal function of cranial nerves (CN) I-V. A left-sided CN VI palsy is present. CN VII displays left-sided upper and lower facial weakness as well as right-sided weakness affecting the lower face.

Functions of CN VIII (left), IX and X are also impaired bilaterally. CN XI and XII are intact. Motor examination of the upper & lower extremities reveals normal tone, power (5/5) and reflexes (2+) bilaterally. There is no pronator drift and plantar responses are normal. Sensory examination is normal to touch and proprioception. Tests of coordination and gait are normal.

Laboratory investigations reveal pancytopenia (Hb 80 with MCV 85.2, WBC 3.6, platelets 125), with a leukoerythroblastic blood film. Phosphate is low (0.53) and ALP is high (1,899) with all other electrolytes & liver enzymes normal. Haptoglobin is 2.48, LDH is 1260, and total bilirubin is 10. Serum ACE is normal (19) and serum protein electrophoresis (SPEP) detects trivial gamma spikes.

Brain MRI shows a soft tissue mass in the clivus and petrous bones on the left, extending into the cerebellopontine angle and causing medullary compression. Evidence of diffuse metastatic disease is seen in the skull and cranial vault. Chest and abdominal CT also report sclerotic skeletal metastases as well as co-existent Paget's disease. A right hilar lymph node of borderline size and right iliac lymphadenopathy are noted. Prostate size measures 4.0 cm x 3.5 cm in dimension.

In considering the presence of malignant disease, a bone marrow aspirate and a prostate-specific antigen test (PSA) are obtained. PSA is reported as 200 and bone marrow aspirate shows infiltration by non-haematopoietic malignant cells.



**What is the diagnosis?**

# And the diagnosis is . . .

## Case 1

**Diagnosis: Metastatic prostate cancer with involvement of clivus and petrous bone.**

### Discussion

Prostate cancer is the most common male cancer in Canada and the third most common cause of cancer death in men.[3,7] Due to the widespread use of PSA screening, most men are diagnosed in the early stages of disease, with minimal-to-absent symptoms. Only an estimated 20-30% of patients present with metastatic disease, and one-quarter of them die from their disease within two years.[3]

Metastatic prostate cancer primarily targets bones and lymph nodes, resulting in symptoms such as back pain and leg weakness.[1] Central nervous system complications may also be seen, affecting the spinal cord and the brain. Spinal cord compression is an oncologic emergency, arising from metastases to the vertebral column or paravertebral space. Presenting as back pain, it may also cause muscle weakness, urinary retention or bladder/bowel incontinence.[2] Brain metastases is rare and occurs in the context of failed androgen deprivation therapy for advanced disease.[2] It is rarely seen in the initial presentation of prostate cancer. Leptomeningeal spread represents the most common intracranial pattern, followed by involvement of the cerebrum and lastly, cerebellum.[2] Solitary lesions are more common than multiple lesions.[6]

Common symptoms associated with brain metastases include headache, altered cognition, focal weakness, seizures, and gait ataxia.[6] Cranial nerve involvement is very rare and only a few cases have been reported. One such case is that of a Collet-Sicard syndrome (i.e. paralysis of the lower four cranial nerves) which presents as prostate cancer metastatic to the temporal bone and jugular foramen.[5] Another describes diplopia and a right sixth nerve palsy as the initial features of a prostate cancer mass in the clivus.[4]

Diagnosis of brain metastases relies on a combination of clinical, radiological, and biopsy-guided assessments. Gadolinium-enhanced MRI is invaluable and more sensitive than CT scanning for detection of multiple intracranial lesions.[2] In addition to a PSA level, patients should also be referred for a TRUS-guided prostate biopsy, bone scan, and CT scan of the abdomen and pelvis to look for other areas of metastases.

Both medical and surgical treatments are available for metastatic prostate cancer and focus on reducing circulating androgen levels, chiefly testosterone. The major source of testosterone is the testes, although a small quantity is also produced from the adrenal glands.[3] Androgen deprivation therapy (ADT) may be achieved medically with LHRH agonists such as leuprolide acetate, surgically with bilateral orchiectomy, or a combination of both, called maximal androgen blockade (MAB).[1] ADT may cause side effects such as depression, hot flashes, osteoporosis and decreased libido, but avoids the cardiovascular toxicity of estrogens such as diethylstilbestrol (DES), which were used routinely in the 1980's.[1]

ADT is associated with improvements in overall progression-free survival. Current guidelines suggest starting monotherapy (orchiectomy or an LHRH agonist) as standard treatment. LHRH agonists appear to be as effective as orchiectomy, while causing fewer side effects and maintaining potency.[3] MAB has not shown convincing evidence of improved benefit over monotherapy and should not be routinely offered.[3]

Despite the success of ADT, most men with metastatic prostate cancer will experience cancer progression in an average of 18 to 24 months.[7] They may display biochemical or radiological progression in the form of rising serum PSA levels and the appearance of new metastases. Disease progression, despite ADT, is termed androgen independence. Symptoms at this stage may be debilitating, including bone pain, pathologic fractures, spinal compression, and bone marrow failure, as well as paraneoplastic effects such as weight loss, hypercoaguability, and increased infections.[7] A variety of palliative interventions are available for patients with androgen independence. Docetaxel-based chemotherapy is the only current treatment that carries survival benefits.[7] Other treatments such as mitoxantrone-prednisone-based chemotherapy, bisphosphonates, ketoconazole, and radiotherapy have not demonstrated survival benefit but play an important role in improving quality of life.[2,7]

### Back to the Case

ADT, corticosteroids, and radiotherapy were offered to the patient. There was modest improvement in symptoms with radiotherapy. Hormonal androgen depletion therapy with bicalutamide and leuprolide resulted in a decrease in PSA from 200 to 54; however, this was not accompanied by a change in clinical disease. Subsequently, palliative care was instituted.

This case illustrates the uncommon occurrence of cranial nerve palsies as a presentation of metastatic prostate cancer.[1] Brain metastasis is rare outside the context of advanced disease and even rarer as a mode of disease presentation. There are only a few cases of cranial nerve involvement, with the current case as the first to report CN VI-X palsies, while sparing the lower two cranial nerves.

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# Quick Diagnosis

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## History

A 56-year-old woman presented to her family physician's office with a three-week history of intermittent fever associated with chills, rigours and headache which worsened at night. She also complained of intermittent shortness of breath, cough, increasing hiccups and burping. The patient was prescribed a seven-day course of amoxicillin without relief and subsequently presented to the emergency room with worsening fever and burping.

The patient was originally from India and had immigrated to Canada six years prior to presentation. Remarkable past medical history included Type II Diabetes diagnosed five years previously, with no known complications, and hypertension diagnosed one year previously. The patient had no record of prior surgeries or hospitalizations. There was no history of blood transfusions, intravenous drug use or other HIV risk factors. Two years before this episode, the patient had experienced microscopic hematuria which resolved spontaneously without treatment. At presentation, the patient was taking glyburide 2.5 mg po bid and lisinopril 5mg po od.

## Physical Examination

On examination, the patient weighed approximately 75 kg. Vital signs were normal with a body temperature of 37.5° C. On respiratory examination she had mild bilateral basilar crackles with no associated wheezing or vesicular sounds. There was abdominal distension but no evidence of ascites or organomegaly. Peripheral examination revealed pitting oedema in the lower extremities up to the knees bilaterally. Musculoskeletal examination revealed Heberden's nodes in the distal interphalangeal joints of all fingers.

## Investigations

Hb = 100 g/L (115 – 160)
WBC = 14.1 (4.0 – 11.0 x$10^9$/L)
Neutrophils = 0.79 (0.42 – 0.77 x$10^9$/L)
Plt = 490 (140 – 400 x$10^9$/L)
MCV = 85 (78 – 98 fL)
Creatinine = 110 (40 – 90 $\mu$mol/L)

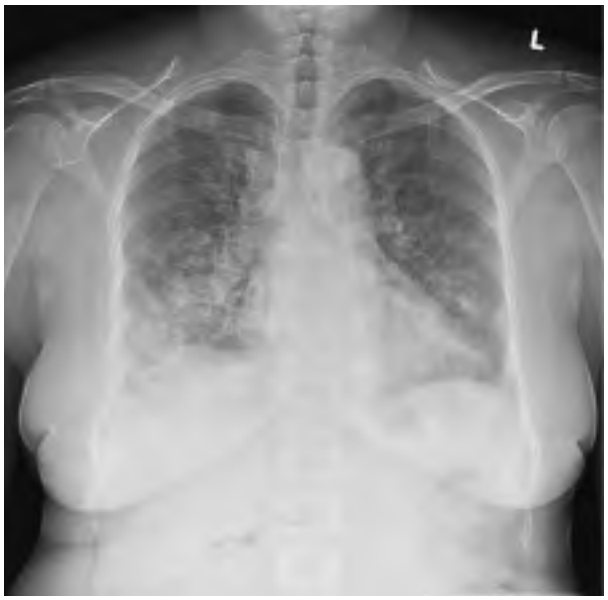


**Figure 1.** Chest X-ray. Poorly defined areas of increased density seen in the lower lung zones bilaterally, including a 2.8 cm rounded density at the level of the diaphragm.

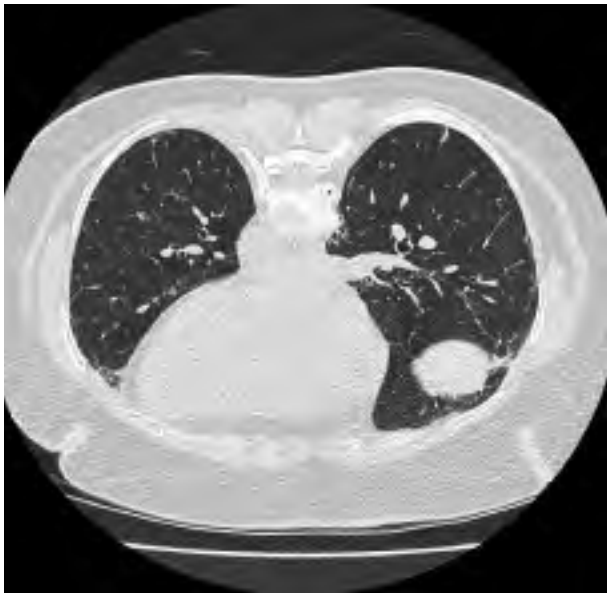

**Figure 2.** Chest CT: CT of chest showing a pulmonary nodule at the lung base measuring 5.2 cm x 2.1 cm

P-Amylase = 71 (<55 U/L)
ALP = 73 (40 – 130 IU/L)
AST = 13 (5 – 40 IU/L)
ALT = 12 (5 – 40 IU/L)
GGT = 14 (5 – 40 IU/L)
Hepatitis B serology: HbsAG negative, Hep B antibody negative

Total bilirubin = 10 (1-17 umol/L)
Albumin = 21 (35-50 g/L)
TSH = 2.46 (0.34 – 5.60 mIU/L)

Ferritin = 87.0 (11.0 – 306.8 ug/L)
Haptoglobin = 4.05 (0.40 – 1.95 g/L)
Random glucose = 7.3 (3.9 – 6.1 mmol/L)
Iron = 4 (7 – 30 umol/L)
TIBC = 30 (45 – 85 umol/L)
% saturation = 13 (20 – 55)
Fecal occult blood = negative
Urinalysis: Leuk neg, nitrites neg, protein 1+, pH 5.5, blood 3+, ketones neg, glucose neg, positive for eosinophilia.
Urine microscopy: 1-3 WBC/hpf, 10-15 RBC/hpf, 1-2 RBC casts/lpf
Urine culture = normal
Blood cultures (aerobic and anaerobic) = normal

Chest X-ray and CT images of the chest and abdomen were obtained (Figures 1 and 2). Enhanced chest CT revealed diffuse bilateral pulmonary nodules and multiple pleural-based masses, with the largest at the left base measuring 5.2 cm x 2.1 cm. Some smaller nodules demonstrated central cavitation. The CT also showed mild bilateral hilar lymphadenopathy, enlarged subcarinal nodes and patchy fibrotic changes at both lung bases.

An abdominal ultrasound revealed bilateral renal cortical cysts up to 2.6 cm in size with no hydronephrosis. A 2D echocardiogram was reported as essentially normal. CT-guided lung biopsy was negative for acid-fast bacilli and fungus. Sputum analysis did not show acid-fast bacilli. During the first week in the hospital, her creatinine increased from 110 to 196 µmol/L and later up to 255 µmol/L. Urea remained normal. A kidney biopsy was done which showed the following:

antiGBM antibodies > 100 (< 7 U/mL)
cANCA < 1.0 (<2.0 U/mL)
pANCA 25.7 (<6.0 U/mL)
C3 1.31 (0.8 – 1.50 g/L)
C4 0.27 (0.15 – 0.38 g/L)
ANA negative, RF negative.

**What is the diagnosis?**

# And the diagnosis is . . .

## Case 2

### Diagnosis: Anti-glomerular basement membrane disease and Wegener's granulomatosis

Anti-glomerular basement membrane disease, classically known as Goodpasture's syndrome, affects type IV collagen in both the lungs and kidneys. Presentation of this disease usually involves pulmonary hemorrhage, rapidly progressive glomerulonephritis or both.[1]

### Epidemiology and etiology

Goodpasture's disease is extremely rare. The incidence is approximately 0.1 cases per million with an equal gender distribution. Disease onset tends to peak bimodally in the fourth and seventh decades of life, but may occur at any age. Although Goodpasture's syndrome is more prevalent in Caucasian populations, particularly the Maoris of New Zealand, the disease is not limited to a particular group.[2]

Coincident Goodpasture's and c-ANCA positive Wegener's disease have been identified in several patients. It is widely suspected that approximately 20-30% of patients with anti-GBM disease will be positive for either c-ANCA or p-ANCA, two antibodies implicated in Wegener's granulomatosis. About three-quarters of these patients have p-ANCA antibodies, while only a small proportion are anti-GBM and c-ANCA positive. Incidence of concurrent Goodpasture's syndrome in Wegener's patients is much less common.[3]

### Pathophysiology

Anti-GBM disease occurs when a patient produces autoantibodies to type IV collagen. The antigen implicated in this disease is the globular NC1 domain of the alpha3 chain of type IV collagen. This molecule is predominantly present in the glomerular and alveolar basement membranes, but is also expressed in the eye, choroid plexus and inner ear.

Contact of autoantibodies with the GBM triggers a complement cascade leading to infiltration of the glomerulus by polymorphonuclear leukocytes and monocytes. Subsequent leakage of fibrinogen through the basement membrane leads to crescent formation and the clinical picture of rapidly progressive glomerulonephritis.

The pathophysiology of Goodpasture's in the lung is less well understood. Since there are no inherent fenestrations in the pulmonary alveolar capillaries as there are in the glomerulus, it is suspected that pulmonary involvement in Goodpasture's syndrome requires coincident pulmonary vascular damage. Smoking and preceding viral or bacterial infection have been associated with increased severity of pulmonary involvement, leading to hemorrhage. As a result of this interaction, patients can present with a wide variety of outcomes, ranging from no pulmonary symptoms to massive hemoptysis, depending on the level of antibody access to the NC1 antigen in the pulmonary parenchyma.

Wegener's granulomatosis is a necrotizing vasculitis of the small- and medium-sized blood vessels, and typically also involves the respiratory tract, lungs and kidneys. Patients often present with cavitary lesions in the lungs; the presence of cytoplasmic or perinuclear antineutrophil cytoplasmic antibodies (c-ANCA or p-ANCA) on immunofluorescence or ELISA confirm the diagnosis.

The etiology of concurrent anti-GBM disease and Wegener's granulomatosis is very poorly understood. It has been suggested that ANCA-related proteases might contribute to exposing the normally hidden NC1 antigen on Type IV collagen. Other hypotheses exist, but none are widely accepted.

### History and examination findings

Diagnosis of Goodpasture's syndrome often follows progression from ambiguous symptoms, such as fever (as in the described patient), fatigue and weakness, to more specific complaints such as blood-streaked sputum, frank haemoptysis, shortness of breath and cough. Complete workup of these patients reveals haematuria, proteinuria and elevated serum creatinine. It is possible for patients to progress to oliguria and acute renal failure within a few weeks secondary to type one rapidly progressive glomerulonephritis.

Physical examination in these patients is typically consistent with their symptoms, but is otherwise unremarkable. Pallor secondary to anemia is common, and respiratory findings such as crackles and wheezing may be present. Patients can have a variety of other findings including oedema, hepatomegaly, hypertension and visual changes, although up to one third of patients have no abnormal findings.[4]

### Differential diagnosis

The differential diagnosis of Goodpasture's syndrome includes solitary Wegener's granulomatosis, systemic lupus erythematosus, necrotizing vasculitis, and Henoch-Schonlein purpura. Patients diagnosed with anti-GBM disease should be further investigated for both p-ANCA and c-ANCA positivity correlating with coexistent Wegener's granulomatosis.

### Management

In the case where investigation of a patient reveals the presence of anti-GBM antibodies and c-ANCA, it is essential to obtain a direct tissue biopsy to determine the relative contribution of both processes to the patient's condition. The treatment for anti-GBM disease involves immunosuppression with high dose steroids and cyclophosphamide as well as plasmapheresis to remove anti-GBM antibodies from the blood. Patients with Wegener's are also treated with steroids and cyclophosphamide, often for a longer duration, but do not require plasmapheresis.

### Acknowledgements

Dr. David Telio and Dr. Matt Heffer for their guidance with the diagnosis, treatment options and support for this article.

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# Generalized Pain

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## Case Presentation

Mrs. A., a 72-year-old woman, presented to the family medicine office with a 2-week history of sudden onset pain, stiffness, and weakness in her neck, hips, and shoulders bilaterally. She described her hip and neck pain to be dull, but her shoulder pain was sharp with her right shoulder significantly worse compared to her left. Provoking factors included movement, especially getting up from a chair, reaching up, or bending down. Furthermore, her pain was worse in the morning than in the afternoon. Fortunately, she did not have pain at rest and she could relieve her pain by walking and taking yoga lessons (3 times/week). Her pain had interrupted her sleep and she felt as if all of her muscles were weakened. She complained of tension headaches and said that she had an extremely stressful summer looking after her autistic grandson. Moreover, she also complained of an episode of tingling in her right-sided lateral thigh, which lasted for several seconds. She had no constitutional symptoms (fatigue, fever, weight loss, night sweats). Additionally, she denied having jaw claudication, severe headaches, or temporal artery tenderness.

Her past medical history was unremarkable except for osteoporosis, for which she took Actonel, and hypercholesterolemia, which was controlled with Lipitor. She did not take any additional medications except for glucosamine, multivitamins, vitamins B/C/D, and calcium. She had no known allergies. She never smoked and she occasionally drinks a glass of wine after supper. Her family history indicated that her mother and uncle had rheumatoid arthritis.

On physical examination, her blood pressure was 140/80 mmHg, her pulse rate was 84 per minute regular, and her aural temperature was 36.6oC. Temporal artery pulsations were palpable bilaterally and her fundi were normal without swelling of the optic disc. On musculoskeletal examination, she had normal range of motion (ROM) and power (5/5) in both sides of her hips and shoulders.

Blood work was performed, including complete blood count (CBC), electrolytes, creatinine kinase (CK), rheumatoid factor (RF), and erythrocyte sedimentation rate (ESR). All of the results were normal except for ESR, which was 40 mm/hr [normal range 0-20].

## And the diagnosis is…

### Diagnosis: Polymyalgia Rheumatica (PMR)

According to Mrs. A.'s history, the most important diagnosis to rule out is giant cell arteritis (GCA) or temporal arteritis, which is a vasculitis that affects medium- to large-sized arteries through immune responses.[1] It is commonly associated with generalized pain in patients older than age 50. Specific signs and symptoms will allow physicians to rule out GCA on history and physical examination. GCA is commonly associated with moderate to severe headache, scalp tenderness, jaw claudication and/or arthralgia, generalized muscle pain, and temporal artery tenderness. Patients with GCA can also present with constitutional symptoms of fever, weight loss, anorexia, and fatigue, which may be mistaken for the presence of malignancy or concomitant infection. Absence of temporal artery pulsations will increase the likelihood of GCA. It is extremely important to rule out GCA since it can cause irreversible blindness secondary to optic neuritis. According to Mrs. A's presentation, she denied the cardinal signs and symptoms of GCA, and thus, a diagnosis of polymyalgia rheumatica (PMR) was considered.

PMR is a clinical condition that affects 0.5% of the population aged 50 years or older. Females with PMR are twice as prevalent as males. It is characterized by severe pain of the neck, shoulder girdle, and pelvic girdle. It is classified as a rheumatic disease, although the etiology is unknown. PMR causes severe pain in the proximal muscle groups; however, no abnormalities are seen on muscle biopsy. Muscle strength and electromyographic findings are normal. Evidence has suggested the presence of cell-mediated injury to the elastic lamina in the blood vessels in the affected muscles.

The patient's history may include symmetrical pain and stiffness in the proximal groups and further discomfort in the upper limbs. There may also be a low-grade fever, weight loss, fatigue, depression, and an abrupt onset of symptoms. The signs and symptoms of PMR are non-specific and may include muscle tenderness, decreased active ROM of joints secondary to pain, and the absence of muscle atrophy.

The diagnosis of polymyalgia rheumatica requires the presence of three or more of the following six criteria: age >65, ESR >40 mm/hr, bilateral upper arm tenderness, morning stiffness >1 hour, onset of illness less than two weeks, depression and/or weight loss.[2]

The only treatment of PMR is medical therapy to suppress autoimmune activity, such as with corticosteroids which have anti-inflammatory properties. Patients taking systemic steroids should be followed closely to avoid systemic side effects or complications. The average length of disease is three years and exacerbations may occur if steroids are tapered too rapidly. Relapse is unfortunately common. The long-term prognosis of polymyalgia rheumatica is good. Many patients can stop their steroid treatment after two years, although some patients may require a small dose of steroids over several years. This is more likely to occur in females, older patients, and those with a higher ESR at diagnosis. Most cases of PMR can be managed within primary care; nonetheless, diagnosis and management may be difficult, especially those with an inadequate response to steroids or a relapse,

and these cases should thus be referred to a rheumatologist.

### Important Note:

The cardinal symptoms of polymyalgia rheumatica – prolonged morning stiffness in the shoulder and pelvic girdles, with an elevated ESR – are relatively easy to recognize. However, PMR should be a diagnosis of exclusion. It is extremely important to note the high association of PMR with GCA. Approximately fifty percent of patients with GCA meet the diagnostic criteria for PMR, and fifteen to twenty percent of patients with PMR have concurrent GCA or will develop manifestations of GCA in the future.[3,4] In any patient who presents with PMR, it is mandatory to ask about headache, scalp tenderness, and jaw claudication, as to avoid irreversible blindness caused by GCA. When in doubt, the patients should be put on higher doses of steroid immediately, before lab results can be obtained. It is also important to order a temporal artery biopsy.

### Back to the Case

Mrs. A's physician decided to start her on a low dose of corticosteroid (15 mg of prednisone per day) before receiving her blood results. At the follow-up appointment 4 days later, and after being on steroids for 4 days, Mrs. A's condition had improved. She described herself to be 100% normal the first day she took the steroid medication. Nonetheless, the effect of steroid declined slowly from 100% to 50%, then to 25%, and on the day of the appointment, 10% of normal. However, the immediate marked improvement of her condition with the use of the steroid significantly narrowed the differential diagnoses, and a presumptive diagnosis of PMR was made.

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# A Complicated Case of Shortness of Breath

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## Case Presentation

Mr. M, a 63 year-old Caucasian man presented to Toronto General Hospital Emergency Department with a five day history of increasing shortness of breath (SOB). He had seen his family physician two days earlier and had received moxifloxacin (Avelox) for a possible respiratory infection. However, his respiratory symptoms continued to increase in severity over the following few days. He was advised by his family physician to seek further investigation and treatment at the Emergency Department. His SOB had been accompanied by occasional cough, but no sputum production or haemoptysis. Because his wife and son had both suffered from upper respiratory tract infections during the past two weeks, Mr. M initially attributed his SOB to a similar cause. However, with the progression of his symptoms beyond those experienced by his family members, Mr. M sought medical attention.

Relevant past medical history includes chronic obstructive pulmonary disease (COPD) treated with salbutamol (Ventolin) and ipratropium (Atrovent). He previously had multiple deep vein thromboses (DVT) with a secondary diagnosis of Antiphospholipid Antibody Syndrome one year prior to the current admission, for which he was taking warfarin (Coumadin) prophylaxis. At the time of the work-up of his thrombophilia, an abdominal ultrasound was performed that incidentally revealed liver cirrhosis. A work-up for the cause of his cirrhosis had not yet been performed. His cirrhosis had since been complicated by moderate ascites, treated with spironolactone (Aldactone) and furosemide (Lasix), as well as oesophageal varicies, which had required banding.

Mr. M was a lifetime non-smoker but had a history significant for second-hand smoke exposure. He had previously consumed 5 to 6 drinks of alcohol per day but had remained abstinent from alcohol since his diagnosis of liver cirrhosis 7 months ago. He had no history of any other drug use. Mr. M lives at home with his current wife and twelve year old son and has two daughters from his previous marriage. He owns and operates a small independent company with his current wife.

In the Emergency Department, Mr. M was afebrile with a heart rate of 109 beats per minute and a respiratory rate of 20 breaths per minute. He was in considerable respiratory distress with an oxygen saturation of 87% on room air. There was a moderate amount of ascites apparent on abdominal examination but the rest of his general physical examination was unremarkable. Routine laboratory investigations revealed leukocytosis, moderately elevated liver enzymes, and a subtherapeutic INR of 1.23. The CT thorax demonstrated hyperinflated lungs, consistent with COPD, with bilateral multiple pulmonary emboli, and nonspecific ill-defined ground-glass opacities suggestive of an inflammatory or infectious process.

## Diagnosis and Treatment

Upon review of the CT thorax, Mr. M was diagnosed with multiple pulmonary emboli. The aetiology of this was presumed to be due to his underlying thrombophilia and subtherapeutic INR. Given that this was his second thromboembolic event in the past year, he was deemed to be a warfarin (Coumadin) failure. He was subsequently treated for his current thromboembolic event and maintained on prophylaxis with tinzaparin (Innohep). It was felt, however, that his clinical presentation was not entirely consistent with pulmonary emboli. He had increasing SOB over the past five days with symptoms of respiratory tract infection and the CT thorax suggested that there might also be an underlying infective process. He was suspected of experiencing a coexisting respiratory tract infection or COPD exacerbation and was additionally treated with IV antibiotics, prednisone, and inhaled corticosteroids. His respiratory distress gradually improved over his 12-day stay in hospital, but he was not yet at baseline at the time of discharge.

## Was Something Else Going On?

During Mr. M's admission, he further disclosed that in addition to the acute event that brought him to hospital, he had been feeling progressively more unwell over the past year. He had been experiencing increasing fatigue, generalized weakness, and rising weight secondary to ascites. These symptoms had become disabling to the point that he was no longer able to manage his business on a daily basis, forcing him to become increasingly reliant on his family for assistance. He was concerned with the ongoing deterioration due to his liver cirrhosis and COPD despite lifestyle and medical interventions and was interested in further investigations and management of these conditions.

Further inquiry revealed that the diagnosis of COPD had been made by his family physician two years earlier when he presented with increasing dyspnea. He was empirically treated with salbutamol (Ventolin) and ipratropium (Atrovent). However, objective documentation of airflow limitation with pulmonary function testing had not yet been performed. Furthermore, although liver cirrhosis had been incidentally discovered the previous year on abdominal ultrasound and its aetiology was presumed to be secondary to alcohol consumption, no further investigations into the aetiology were performed.

A detailed family history revealed that his father had died in his thirties from accidental death. Three of his paternal uncles died from complications of liver cirrhosis and one uncle had COPD. His paternal grandfather had also died of complications from liver cirrhosis and had COPD.

## What is the Diagnosis?

### Diagnosis: Alpha-1-antitrypsin Deficiency

Alpha-1-antitrypsin (AAT) deficiency is an inheritable disorder that can affect the lungs, liver, and rarely, the skin.[1] AAT is a serine protease inhibitor and abnormalities in this protein lead to the distinct clinical manifestations of the disease.[2]

In the lung, deficiency of AAT predisposes to COPD, especially panacinar emphysema. Lung disease in AAT deficiency is thought to result from an imbalance between neutrophil elastase, which destroys elastin, and AAT which acts as an elastase inhibitor and protects against proteolytic degradation of elastin.[3,4,5]

Hepatic disease due to AAT deficiency can manifest as neonatal hepatitis, cirrhosis in both adults and children, and hepatocellular carcinoma.[6,7,8] The pathogenesis of the liver injury in AAT differs from that of pulmonary disease. Liver disease is caused by pathologic polymerization of the abnormal AAT, resulting in intrahepatic accumulation of AAT molecules, activation of autophagy, mitochondrial injury, and endoplasmic reticulum stress causing hepatocelllar injury.[9,10,11]

A rare clinical manifestation of AAT deficiency is necrotizing panniculitis. This is characterized by inflammatory lesions of the skin and subcutaneous tissue.[12] The pathogenesis of panniculitis is similar to that of emphysema and is thought to result from unopposed proteolysis in the skin.[13]

Screening for AAT deficiency can be done by measuring the serum AAT level. A positive screening test is considered a serum AAT level below the protective normal range of 0.90 g/L to 2.0 g/L.[14] Definitive diagnosis of the disease is done with AAT phenotyping.[15]

The AAT protein is encoded by a gene on the long arm of chromosome 14.[16] At least 100 alleles of AAT have been identified and given a letter code based on electrophoretic mobility. The family of normal alleles is referred to as M and the normal phenotype is MM. The two most common deficient alleles are the Z allele and the S allele. Much less common are the Null alleles, which lead to zero detectable AAT protein in the plasma.[17] AAT deficiency follows an autosomal recessive disease pattern; however, there have been reports of heterozygotic manifestation.[18,19,20]

It is important to note that the different phenotypes associated with AAT deficiency have varying clinical manifestations.[21] All individuals with plasma AAT levels below the minimum protective threshold of 0.90 g/L are considered to be at increased risk for emphysema. There is, however, clinical heterogeneity in respect to the relative risk, onset, and severity of disease for different phenotypes. The most severe forms of lung diseases manifest in the null and ZZ phenotype, in which plasma AAT levels are undetectable or only 0.3 g/L to 0.4 g/L respectively.[22] Furthermore, only those individuals with the abnormal Z allele for AAT are at risk for developing liver disease, as only this protein product is susceptible to polymerization.,

Confounding risk factors also have a significant role in the development of both lung and liver disease in individuals with AAT deficiency. Important risk factors for the development of emphysema include occupational dust exposure and cigarette smoking.[25,26,27] Risk factors for the development of advanced liver disease in individuals with phenotypically susceptible AAT deficiency include male gender and obesity. Alcohol use and viral hepatitis, however, do not appear to increase the risk of progressive hepatic failure.[28]

### Is Investigation for Alpha-1-Antitrypsin Deficiency Indicated in this Case?

Although AAT deficiency can be an underlying cause of Mr. M's chronic diseases, the possibility of AAT deficiency had never been considered. The most likely reason that further etiologic investigations had not been performed is that he also had significant lifestyle risk factors for both COPD and cirrhosis. Furthermore, AAT deficiency presents as coexistent pulmonary and liver disease in less than 10% of cases.[29]

AAT deficiency is considered to be a rare inheritable condition, however, several studies indicate that this disorder is far more prevalent than most physicians realize and often goes unrecognized.[30] AAT deficiency occurs worldwide, but its prevalence varies by population. The highest risk groups occur in Scandinavia and the disorder is much less common in Asian and African populations. In North America, direct population screening studies indicate that the prevalence of individuals with severe AAT deficiency ranges from 1 in 1575 to 1 in 5097, which is approximately equivalent to the prevalence of cystic fibrosis.[31] The under-recognition of AAT deficiency has been shown to lead to delayed diagnosis of the disease. One study demonstrated that for individuals with severe AAT deficiency, there is an average delay of 7.2 years from onset of symptoms to diagnosis, and on average these patients report seeing between six and ten physicians before the appropriate diagnosis has been made.[32] It is imperative to identify individuals affected by AAT deficiency, as disease-specific therapies exist.[33] Furthermore, appropriate diagnosis of this genetic disease will allow for the screening of relatives of known cases and, if found to be AAT deficient, these individuals can be counselled to eliminate modifiable risk factors before the development of symptomatic disease. Thus, it is important that physicians maintain an index of suspicion for AAT deficiency and initiate investigations for the disorder when appropriate.

### Back to the Case

Given Mr. M's history of both COPD and liver cirrhosis and his family history of both of these diseases, a serum AAT level was ordered to further investigate the aetiology of his underlying conditions. His serum AAT level was determined to be 0.20 g/L, well below the normal range of 0.90 g/L to 2.0 g/L. Subsequent investigations determined his AAT phenotype to be protease inhibitor type ZZ. This abnormal phenotype is known to produce deficient levels of serum AAT, resulting in elastase destruction in the lung, and causes polymerization of AAT protein in the liver, which leads to hepatic disease.

### Treatment of AAT Deficiency

Treatment of pulmonary manifestations of AAT deficiency is initially similar to the treatment of non-AAT-related emphysema, including risk factor modification, bronchodilators, and corticosteroids. More recently, specific therapy includes providing exogenous pooled human AAT.[34] This treatment, known as intravenous augmentation therapy, is aimed at rais-

ing the plasma level of AAT above the protective threshold to prevent the progression of lung disease.[35] However, the benefit of AAT augmentation therapy is inconclusive, as clinical trials have been limited by the relatively low prevalence of the disease as well as the excessive cost associated with using this therapy on large populations. The expense of augmentation therapy also limits its use in patients since this treatment is not covered by provincial drug plans in Canada.

Furthermore, the optimal time for the introduction of augmentation therapy has not been established. In theory, starting therapy early might produce benefits by preventing disease progression, however, there is insufficient data to support this in clinical practice. Future therapies may include aerosolized augmentation therapy, enhancement of endogenous AAT production, and gene therapy.[36,37,38,39] Individuals with severe pulmonary disease may also be eligible for lung transplantation with the possibility of augmentation therapy after transplantation.[40]

Fewer treatment options exist for individuals with AAT deficiency-associated liver disease. Treatment is currently aimed at risk factor reduction and supportive therapy for the complications associated with liver disease. Patients with end-stage hepatic disease are eligible for liver transplantation. Liver transplantation has the additional advantage of correcting the AAT level since the normal phenotype donor liver produces and secretes AAT, which potentially protects from, or prevents the progression of, the pulmonary manifestations of the disease.[41]

## The Outcome for Mr. M

Unfortunately, over the following six months, Mr. M's liver function greatly deteriorated. He developed marked ascites, despite diuretic use, and experienced multiple episodes of hepatic encephalopathy. Subsequently, he and his hepatologist decided it was appropriate to move forward with liver transplantation. Mr. M and his wife are presently undergoing investigations in preparation for live donor liver transplantation.

Concurrently, his pulmonary function deteriorated slightly and his FEV1 decreased from 67% of predicted to 61% of predicted; however, he remained clinically stable and was not experiencing increased SOB. His pulmonary disease was not yet severe enough to require AAT augmentation therapy. Furthermore, with hopes of a successful liver transplant, AAT augmentation therapy may not be required in the future once his plasma levels of endogenous AAT reach a normal protective level.

## Take Home Points

1. AAT deficiency is under-recognized by physicians; however, it is important to maintain an index of suspicion for the disorder as it is an inheritable condition and screening can be initiated in relatives of affected individuals.
2. Screening for AAT deficiency can be done by measuring the serum level of AAT and definitive diagnosis of the disease can be made through AAT phenotyping.
3. The major clinical manifestations of AAT deficiency include emphysema, liver cirrhosis, and rarely, panniculitis of the skin. However, different phenotypes of the disease have varying presentation.
4. The pathophysiology of pulmonary disease is due to a deficiency of the AAT protease inhibitor leading to elastin destruction. Liver disease is due to a pathologic polymerization of the abnormal AAT protein causing hepatocellular injury.
5. Therapy for complications of AAT is initially similar to that of COPD and cirrhosis of other causes. Disease-specific therapy exists for the pulmonary manifestations of AAT, although further studies are needed to establish its clinical utility.

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# A Batty Progression of Developmental Milestones

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## Case Presentation

A four-and-a-half-year-old boy presents to his paediatrician with concerns about his development. His mother is worried that her son is not reaching expected developmental milestones. The boy had previously been diagnosed with a primary seizure disorder at the age of three-and-half-years, and these seizures have increased in frequency over the past year.

Until recently, there had been no concerns with his development. He was able to sit unsupported at 6-months of age and walk at 13-months of age. He was able to use the bathroom with little assistance and he had previously been able to name shapes and colours. The boy's mother noticed a regression in milestones that began one year ago, along with the onset of his seizures.

Currently he has significant problems with both gross and fine motor skills. He has started to fumble with objects and has become clumsy with frequent falls. He is no longer progressing with his speech and language development, and he has had some recent behavioural changes, such as biting others when frustrated. He finds it difficult to find small objects and to recognize faces, which raises concerns about his vision.

His perinatal period was normal and he was born by spontaneous vaginal delivery, at term, with no birth complications. There is no family history of developmental delay and no history of consanguinity. The child's only significant medical history was a primary seizure disorder, diagnosed at the age of three-and-a-half, which was initially controlled with valproic acid (Valproate). In the past few months, the frequency of seizures has increased.

The boy had normal vital signs, was within normal height and weight parameters for his age, and he did not exhibit any dysmorphic features. He was unable to make appropriate eye contact with the physician and was not verbalizing. His head and neck exams were normal. On ophthalmologic exam his retinas were darkened on the medial side. His cardiovascular, respiratory, and abdominal exams were unremarkable.

Neurological exam revealed a stiff and awkward gait, and there was one incidence of falling while in the physician's office. There was no nystagmus. He had increased muscle tone bilaterally in both the upper and lower extremity with generalized accentuated reflexes.

The patient's EEG displayed spike-slow wave complexes either generalized or restricted to either hemisphere. Possible photic paroxysmal response was also noted. Initial tests for lactate, very long chain fatty acids, organic acids, mucopolysaccharides, and oligosaccharides were normal. An MRI revealed moderate cerebellar and cerebral atrophy, predominantly involving the frontal lobes, and global ventriculomegaly was quite evident.

## The Diagnosis: Batten's Disease – Late Infantile Category

Batten's disease or neuronal ceroid-lipofuscinoses (NCL) refers to a cluster of neurodegenerative disorders that presents in childhood.[8,9,10] It is a rare, yet fatal, condition which affects 2-4 out of 100,000 live births.[10] It was first described by Dr. Otto Stengel in 1826.[10] However it was Batten, in 1903, who made the first correlation between its presentation and pathology.[10,11] Since then, several distinct neurological conditions have fallen under the generalized term, "Batten's Disease" or NCLs. Major categories of NCL include congenital, infantile, late infantile, and variants of late infantile.[8,9,10,11]

## Congenital NCL

A total of only 10 cases of congenital NCL have been described in the literature.[10] Infants usually present with congenital microcephaly, status epilepticus, and respiratory distress.[1,10,11] The condition is fatal within the first few weeks of life.[2,11]

## Infantile NCL

Children will usually attain normal developmental milestones for the first year.[10,11] By the second year of life, however, ataxia, muscle clumsiness, and visual problems become apparent.[9,10,11] By the third year of life, most patients have lost their vision and motor capabilities, and have become socially withdrawn. Increasing seizures and myoclonias predominate until death before the first decade.[9,10,11,12]

## Late Infantile NCL

Children afflicted with late infantile NCL first manifest symptoms by the third year of life.[10,11] Symptoms are characterized by the sudden onset of epilepsy or psychomotor retardation. The seizures are most frequently tonic-clonic in nature and are resistant to medical therapy.[9,10,11] Visual loss is a late manifestation of late infantile NCL and is often partial in nature.[10,11]

Nearly all Batten's disease and associated syndromes are autosomal recessive in nature.[13] They occur as a result of mutations in the CLN gene series, which code for the enzyme palmitoyl protein thioesterase 1 (PPT1).[9,13] Abnormal versions of PPT1 cause excessive lipopigments to deposit primarily in the brain, eyes, and muscles, which leads to clinical manifestations, progression and premature death.[10,13]

A definitive diagnosis of Batten's can be reached through characteristic changes in MRI and EEG. Imaging via CT or MRI reveals progressive atrophy of the cerebrum and cerebellum.[10] EEG abnormalities include occipital spikes with photic stimulation, spike and slow-wave complexes, and overall disorganization.[10] Decreased enzyme levels of palmitoyl protein

| Onset | Symptoms |
|---|---|
| **Early Onset** (Newborn or young infant) | Intermittent lethargy, decreased responsiveness associated with episodes of emesis<br>Irritability, excessive or absent startle response<br>Decreasing interest in surroundings, excessive sleepiness, decreased smiling<br>Poor or absent eye fixation, presence of nystagmus<br>Poor head control, weak suck<br>Feeding difficulties, failure to thrive<br>Excessive tongue thrusting, asymmetric movements, unusual posturing<br>Floppy or spastic tone<br>Seizures |
| **Later Onset** (Older infant or child) | Change in temperament, behaviour, or activity level<br>Disturbance in gait (especially progressive ataxia), clumsiness<br>Unusual movements, dystonia, chorea<br>Progressive muscle weakness, muscle hypo/hypertonia<br>Progressive loss of speech, vision, or hearing<br>Complaints of headache<br>Changes in bowel/bladder<br>Seizures |

**Table 1.** Symptoms of Progressive CNS Disease[9]

thioesterase (PPT) or tripeptidyl peptidase 1 (TTP1) can also be investigated in leukocytes, cultured fibroblasts, dried blood, and salivary samples.[9,10,13]

There is no curative medical treatment available for Batten's disease.[10] Currently, patients receive palliative care for their seizures and are given standard anticonvulsants.[8,10] The efficacy of bone marrow transplants, stem cell transplants, vitamin E, and selenium are under investigation, while current animal models have not yielded positive results.[10] Current research involves experimentation with the adeno-associated virus gene transfer vector of the CLN gene series.[10,13]

## Developmental Delay: The Clinical Approach

Delay in attaining milestones in one or more areas of development is a frequent concern voiced by parents. In the assessment of these patients, the first important aspect to consider is whether the developmental delay exists, or if their development merely represents normal variation within a population. Once true developmental delay is established, the next important differentiation is whether the underlying disorder is static, which requires less urgent evaluation, or a progressive neurologic process requiring prompt evaluation for a possible neurodegenerative disorder.[3]

A thorough developmental history should be obtained, which documents the chronology of attainment of all expected milestones. It is important to ascertain whether the child is affected in one area of development or if the process is generalized. One must determine the moment at which concerns with development first became apparent. Developmental concerns that were present during prenatal screening or during the neonatal period are more suggestive of a static process, while developmental delay that is preceded by a period of normal development is more concerning for a progressive neurodegenerative process.[4] Loss of previously acquired abilities is also an important differentiating factor for static versus progressive process. This is an extremely concerning feature on the history of a patient with developmental delay, since developmental regression is often the hallmark of neurodegenerative disorders.

A review of prenatal and birth history may provide further clues as to the aetiology of a child presenting with developmental delay. Such an assessment should include questions regarding previous pregnancies, miscarriages, or spontaneous abortions, as well as any maternal disease, medications, or abnormal prenatal findings during pregnancy. Review of the child's birth parameters and neonatal course may also provide an explanation for the given developmental delay. For example, a child who presents with gross motor delay with a history of significant asphyxia at birth and abnormal umbilical cord blood gases is more likely to have a static developmental delay due to early neurologic insult.[6] It should be noted that a significant birth history does not rule out a neurodegenerative disorder and that further investigation is required if more concerning symptoms, such as developmental regression, are also present.

Exploration of any associated symptoms in the child who presents with developmental delay is critical in differentiating static versus progressive neurodegenerative disorders. A list of these concerning associated symptoms can be seen in Table 1. Furthermore, a comprehensive review of systems is necessary in children with developmental delay as many of the progressive neurodegenerative disorders are multisystem diseases.[7]

Family history is helpful for distinguishing a genetic aetiology for developmental delay. It is also important to determine if there is consanguinity between parents, as many of the progressive neurodegenerative disorders display an autosomal recessive pattern of inheritance.[8]

## Developmental Delay: The Physical Exam

The physician should begin their physical assessment by a general assessment, paying particular attention to the developmental level of the child. A full physical examination is necessary. Important features of examination in progressive neurodegenerative disease can be seen in Table 2. Physical examination abnormalities may also be evident in many causes of

static neurologic disorder, such as cerebral palsy. Comparison to earlier physical examination results, however, will most likely reveal abnormalities that have been persistent over time.

Any child with a clinical history suggestive of a progressive neurologic process should be initially investigated with electroencephalography (EEG) evoked potentials, CSF testing, and brain imaging.10 The differential diagnosis (under central nervous system degenerative disorders of childhood) would include Adrenoleukodystrophy, Batten's disease, Dawson's disease, Megalencephalic leucodystrophy, Alexander disease, and many others.[8,9,10] Since neurodegenerative disorders are quite rare, however, and often arise from increases in certain substrates, a thorough biochemical assay is essential for a definitive diagnosis.[10] A paediatric neurologist is experienced in the appropriate investigations to facilitate such a diagnosis.

| Organ/System | Features |
|---|---|
| **Head** | Head circumference<br>Micro/macrocephaly<br>Fontanelle size, possible bulging<br>Sutures open, split, closed, asymmetric |
| **Face** | Coarse features |
| **Eyes** | Corneal clouding<br>Cataracts |
| **Cardiopulmonary** | Murmurs |
| **Gastrointestinal** | Hepatosplenomegaly |
| **Skin** | Pigmented/hypopigmented<br>Vascular or eruptive lesions<br>Sacral dimples or hair tufts |
| **Other** | Body/urine odour |
| **Neurologic (age dependent)** | |
| Mental Status | Alertness/responsiveness<br>Interaction with examiner<br>Language skills |
| Cranial Nerves | Visual acuity<br>Pupillary response<br>Eye movements<br>Nystagmus<br>Hearing acuity<br>Tongue fasiculations<br>Fundi (optic disc blurring, optic disc atrophy, cherry red macula) |
| Motor System | Proximal and distal (hypo/hypertonic) muscle tone<br>Presence or absence of hemiatrophy<br>Tremor or fasciculation at rest<br>Gait (ataxic, spastic)<br>Proximal and distal muscle strength<br>Cerebellar testing<br>Stretch reflexes, hypo/hyper-reflexia, clonus, reflex asymmetry<br>Babinski sign<br>Primitive reflexes |

**Table 2** Important Features on Examination in Progressive CNS Disease[7]

## Case Outcome and Prognosis

Since his initial presentation, this child has been managed with increasing doses of valproic acid (Valproate) and carbamazepine (Tegretol) for his seizures. As he progresses in life, he will gradually lose all psychomotor abilities. With the loss of swallowing, artificial feeding will be required. The average life expectancy for a late-infantile NCL afflicted individual is between 10 to 15 years.10,11

## Take Home Points in Developmental Delay

1. When assessing developmental delay, it is essential to first evaluate whether the delay is truly present or simply part of normal variation.
2. Once delay is established, it must be ascertained whether it is focal or global in nature.
3. Clues to the aetiology of the delay can be revealed from pregnancy, perinatal, and family history.
4. It is important to remember that delay preceded by normal developmental milestones is more sinister than congenital delay.
5. Progressive developmental delay in a child requires urgent attention when compared to a static presentation.

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# A Case of Acute Abdominal Pain

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**Abstract**

This paper outlines the case of Mrs. O., a 48 year-old Japanese woman who presented to the emergency department complaining of progressive epigastric pain over the past 4 days, worsening acutely over the last 12 hours. This case serves as a reference point for a discussion of acute pancreatitis. The discussion covers aetiology (including alcoholic, gallstone, and autoimmune pancreatitis), typical symptoms and signs, the role of laboratory investigations such as serum amylase and lipase, the rational use of imaging modalities and investigations including endoscopic retrograde cholangiopancreatography, the clinical utility of severity prediction tools such as Ranson's criteria, treatment options (including fundamentals of treatment such as fluid resuscitation, adequate analgesia, and keeping the pancreas at rest), and complications of both the disease and certain therapies (ie. endoscopic retrograde cholangiopancreatography).

## Case Presentation

A 48 year-old Japanese woman presented to the Emergency Department with complaints of epigastric pain for the past 4 days progressively worsening over the previous 12 hours. The pain was initially post-prandial and of gradual onset, associated with nausea and one episode of non-bloody emesis. The quality of the pain was described as a "pulling" epigastric discomfort, initially rated by the patient as 2/10 pain, and non-radiating. There were no fever, chills, night sweats, cough, shortness of breath, or heart palpitations. The patient's bowel movements had remained normal, without blood or melena, and until the onset of the pain her appetite was described as "good". She had not noticed any change in the colour of her skin or of her sclera. The day before presenting to the hospital, the pain became severe such that it woke her from her sleep. It remained a constant epigastric "poking" pain, judged to be 8/10 in severity, and now radiated into her back. The progressive nature of the pain caused her to come to hospital. On questioning, she complained of some shortness of breath, which she attributed to the pain. She had never experienced this pain before and her past medical history was unremarkable. She had no history of, or risk factors for, coronary artery disease and was on no medications except the occasional ibuprofen for headaches. She was a non-smoker, did not use any recreational drugs, and stated her alcohol consumption was 3 glasses of wine per week, usually no more than one glass with dinner.

On examination, the patient appeared her stated age and was not in visible distress. Her vital signs were stable with a heart rate of 74 beats per minute, blood pressure 113/70, and respiratory rate of 20 breaths/minute. Her temperature was 36.2 degrees Celsius and oxygen saturation was 98% on room air. The cardiac exam was normal. Auscultation of the precordium revealed no extra heart sounds or murmurs. Jugulovenous pressure (JVP) was 3 cm from the sternal angle. Auscultation of the chest was clear, with no crackles or wheezes. The abdominal exam revealed no stigmata of chronic liver disease or abdominal distension. Bowel sounds were present, percussion suggested a normal pattern of bowel gas, and palpation revealed a soft abdomen with mild to moderate tenderness over the patient's epigastrium but no rebound tenderness There were no masses or hepatosplenomegaly detected.

Laboratory investigations revealed a normal hematologic profile and normal serum electrolytes, creatinine, urea (ie. BUN), and glucose. Her total calcium was slightly low at 1.87 mmol/L (normal range 2.18-2.63 mmol/L); total cholesterol and triglycerides were slightly elevated at 5.44 mmol/L and 3.01 mmol/L, respectively. Her amylase, however, was elevated at 681 U/L (normal range 25-125 U/L) and her lipase was elevated >3000 U/L (normal range 7-59 U/L). An electrocardiogram (ECG) was normal. An abdominal ultrasound showed a normal pancreatic duct measuring 2mm in body, with no mass and no stone present. No biliary dilatation was seen, and a normal gall bladder was noted with no stones visualized. An abdominal CT revealed a 4mm stone in the distal pancreatic duct but no dilatation of the pancreatic or common bile ducts, and no peripancreatic inflammatory changes. The radiologist felt that the finding of the pancreatic "stone" may have been an artefact.

## Discussion

**Acute pancreatitis** is an acute inflammatory process that may be confined to the pancreas but can involve peripancreatic tissues and, in severe cases, can have systemic manifestations affecting many organ systems.

The main causes of acute pancreatitis are gallstones (30-60% of cases in most series) and chronic alcohol use. An alcoholic aetiology (~30% of all cases) is, by definition, a chronic problem but may be complicated by acute pancreatitis in the form of a first presentation or acute exacerbation, and should be kept in mind. In the case of gallstone pancreatitis, it is the passage of gallstones through the ampulla of Vater that causes pancreatitis, although the exact mechanism is unclear. This means, however, that in many

patients who present with gallstone pancreatitis, the offending stone has already passed (though there may be additional stones in the gall bladder or common duct). The reason why and the mechanism by which only 10% of chronic alcoholics develop attacks of acute pancreatitis is also not known.[1] Overall, the pathogenesis of this disease is still not well understood. Acute gallstone pancreatitis occurs more often in women, while alcoholic pancreatitis occurs more often in men.[2] Other possible causes of acute pancreatitis include biliary sludge (i.e. microlithiasis), an idiosyncratic drug reaction, dyslipidemia, hypercalcemia, viral infections, abdominal trauma, etc.

Autoimmune pancreatitis is an uncommon type of chronic pancreatitis that has only been described in recent years, but may be important to keep in mind in the context of this case. The incidence is highest in Japan, although recent reports describing it in Europe, Korea, and the US suggest that it is a worldwide entity.[3,4] One study of autoimmune pancreatitis prevalence in Japan reported that 95% of affected patients were over age 45 years, and men were 2 to 3 times more likely to be affected than women.[5] A pancreatic biopsy is required for diagnosis, but it is also supported by elevated serum levels of IgG4, characteristic radiological findings, and response to corticosteroids. Although it is a rare diagnosis, recommendations indicate that it is increasingly important to keep in mind. This disease can present with features suggestive of pancreatic cancer as well as "ordinary" chronic or acute pancreatitis. A correct diagnosis can help avert the consequences of progressive disease and unnecessary surgery (in the setting where the presentation suggests pancreatic cancer). Indeed, autoimmune pancreatitis shows a dramatic response to oral steroid therapy, in contrast to ordinary chronic pancreatitis.

The cardinal symptom of acute pancreatitis is abdominal pain, usually epigastric, acute in onset, and moderate to severe in most patients. The pain usually worsens for the first few hours and then plateaus, lasting several hours to days. It radiates commonly to the back due to the retroperitoneal position of the pancreas, but may also radiate to the flanks, chest, shoulders, and lower abdomen. In some patients, pain may lessen when leaning forward or drawing the knees upwards. In character, the pain is steady and boring, not colicky. Painless pancreatitis is an uncommon but a well-recognized entity. Nausea, vomiting, and fever are other common signs. Fever in the first week of acute pancreatitis (which may go up to 39 degrees Celsius) is due to acute inflammation and is mediated by inflammatory cytokines. The fever will subside as the pancreatic inflammation "cools off." Fever in the second or third week in patients with acute necrotizing pancreatitis is usually due to infection of the necrotic tissue, which is associated with a high mortality and may require surgical intervention.[6]

Signs of acute pancreatitis on physical examination can be varied and diverse depending on the severity of disease. In mild disease, the only sign may be minimal tenderness over the epigastrium. Abdominal tenderness and distension may be present. Cullen's and Grey-Turner's signs, which are ecchymosis around the umbilicus and flanks, respectively, occur in only 1% of cases and are not specific or diagnostic. They are, however, indicative of intraabdominal and retroperitoneal hemorrhage and are associated with a poor prognosis. Cardiovascular abnormalities may include tachycardia and hypotension; respiratory abnormalities may include dyspnea, atelectasis with basal crepitations, and even respiratory failure in severe cases (e.g. respiratory distress syndrome). Obstruction of the common bile duct, secondary to choledocholithiasis, or oedema of the head of the pancreas can cause jaundice.[2,7]

No single laboratory or clinical sign is pathognomonic for acute pancreatitis. While clinical suspicion is a hugely important part of the diagnosis, this must be confirmed with biochemical, radiological, and in rare occasions, histological evidence. Serum pancreatic enzyme measurement is the "gold standard" for the diagnosis of acute pancreatitis, with lipase being more sensitive compared to amylase (in one in-depth review, 92% versus 83%, respectively), and not surprisingly, given the frequent hyperamylasemia found in several extrapancreatic diseases (e.g. salivary glands), more specific as well (96% versus 88%, respectively).[8] Nonetheless, lipase has historically been less frequently ordered than amylase because lipase measurements have been difficult to perform and lacked precision. Serum amylase rises within 6-12 hours of symptom onset and is usually elevated for 3-5 days to a level more than 3 times the upper limit of normal in acute pancreatitis. Serum lipase will remain elevated longer than amylase due to its longer half-life and slower renal clearance. A lipase of 3 times the upper limit of normal is approximately 98% specific for acute pancreatitis.

Radiologic imaging is important in establishing the diagnosis of acute pancreatitis, determining the cause, assessing severity, detecting complications, and guiding therapy. Contrast-enhanced CT is the most accurate imaging modality for the diagnosis of pancreatitis, assessment of severity, and detection of complications.[7] Transabdominal ultrasonography is used mainly for detection of cholelithiasis, and is ordered routinely for most patients. For the detection of dilated bile ducts from biliary obstruction, transabdominal ultrasound has a sensitivity which ranges from 55 to 91 percent. Other imaging studies have increased sensitivity for choledocholithiasis, including endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography ( ERCP), which remains the gold standard.

EUS allows for positioning of the ultrasound transducer in the second part of the duodenum, which eliminates interference from digestive gas or abdominal fat, and most studies report the sensitivity of EUS to range from 88 to 97 percent with a specificity of 96 to 100 percent.9 Some physicians will prefer to use the less invasive EUS to evaluate patients for possible gallstone pancreatitis when the severity is mild and urgent ERCP is not indicated. There are studies suggesting that early ERCP does not appear to be beneficial in patients with acute biliary pancreatitis without obstructive jaundice or biliary sepsis, and oftentimes the patient will have already passed the offending stone by the time he/she seeks medical attention. In such cases, ERCP with sphincterotomy (performed to allow easier passage of additional stones) seems unwarranted since it is not without complications and morbidity. Yet, it is difficult to tell which patients have passed a stone and which have retained common bile duct stones. Up to 50 percent of patients with suspected gall-

stone pancreatitis without jaundice will have choledocholithiasis when investigated, and some of these patients will experience clinical deterioration ultimately requiring urgent ERCP and sphincterotomy.[9] ERCP can also be helpful in the evaluation of other less common causes of pancreatitis such as pancreas divisum, and pancreatic duct strictures. Urgent (within 24-48 hours) therapeutic ERCP is sometimes indicated in patients at risk for or with evidence of biliary sepsis, severe pancreatitis with biliary obstruction, cholangitis, elevated bilirubin, worsening and persistent jaundice, or signs of worsening pain in the setting of an abnormal abdominal ultrasound examination. Morbidity and mortality are reduced with the use of early selective ERCP in patients with severe gallstone pancreatitis.[10] Magnetic resonance cholangiopancreatography (MRCP) is a newer technique, which is noninvasive and lacks the complication of nephrotoxicity; it has also been found to be as accurate as contrast-enhanced CT in predicting the severity of pancreatitis and identifying necrosis. However, unlike ERCP, there are no interventional options with MRCP.

There exist several multi-factorial decision-making tools designed to risk-stratify patients and guide treatment, including the Acute Physiology and Chronic Health Evaluation (APACHE II) scale, the Imrie scoring system, and Ranson's criteria. These form an essential part of every evaluation of acute pancreatitis, but it must be remembered that the accuracy of these systems is not reached until 48 hours after admission, and indeed, according to one recent review, their predictive accuracy is limited.[10] For example, an Imrie score of ≥3 has a positive likelihood ratio (LR) of 4.6 and a negative LR of 0.36 for clinical outcomes of mortality, severity, and pancreatic fluid collections; a Ranson's criteria score of ≥4 has a positive LR of 2.5 and a negative LR of 0.47 for clinical outcomes including major complications, severity, organ failure, pancreatic necrosis, mortality, and longer hospital stay. (See Table 1: Ranson's criteria)

While some patients with mild pancreatitis may need only brief hospitalization and others will be critically ill and require intensive care, certain principles apply to the treatment of all forms of pancreatitis. The cornerstones of management in acute pancreatitis are pain control, intravenous fluids, and keeping the pancreas at rest. In fact, the majority of patients with mild pancreatitis will require only these supportive measures and should recover well enough to be eating within 5-7 days. Adequate pain control should consist of opiates analgesia. Adequate intravenous fluid resuscitation may be necessary in severe disease with hypotension and fluid sequestration.[11,12]

In severe acute pancreatitis, a major complication is pancreatic necrosis, which can lead to the previously mentioned systemic effects including organ failure, cardiopulmonary insufficiency, renal failure, and GI bleeding. Patients who subsequently develop infected necrosis tend to have more extensive necrosis. There are three approaches to reducing the incidence of these bacterial infections: early enteral feeding (if tolerated), selective decontamination of the gut with non-absorbable antibiotics, and prophylactic systemic antibiotics. Other local complications include fluid collections (no action usually required), pseudocyst (usually associated with chronic pancreatitis but can occur in severe pancreatitis), abscess (surgical consultation advised although non-surgical treatment with percutaneous drainage may be a reasonable option, and appropriate antibiotics), and haemorrhage (supportive treatment; surgery if severe unremitting).

| | |
|---|---|
| **At 0 hours:** | |
| Age | >55 |
| White blood cell count | >16,000/mm$^3$ |
| Blood glucose | >11.1 mmol/L |
| Lactate dehydrogenase | >350 U/L |
| Aspartate aminotransferase (AST) | >250 U/L |
| **At 48 hours:** | |
| Hematocrit | Fall by ≥ 10% |
| Blood urea nitrogen | Increase by ≥ 1.8 mmol/L despite fluids |
| Serum calcium | <2 mmol/L |
| pO2 | <60 mmHg |
| Base deficit | >4 MEq/L |
| Fluid sequestration | >6000 mL |

**Table 1.** Ranson's criteria[14]
1 to 3 criteria fulfilled represents mild pancreatitis; the mortality rises significantly with 4 or more criteria fulfilled

## Back to the case

The patient was treated with rehydration therapy and morphine as needed. Her symptoms greatly improved over the next 3 days. ERCP with sphincterotomy to ensure drainage of her common bile duct was then performed and a normal ampulla, common duct, and cystic duct were visualized. No stone was seen. The therapeutic endoscopist was unable to cannulate the pancreatic duct at the time, but sphincterotomy would have ensured a good chance of allowing the reported pancreatic duct stone to pass the ampulla; a follow-up ERCP was booked for the next month and was normal.

4 hours post-ERCP, the patient developed severe recurrence of epigastric pain radiating to the back. Physical examination was remarkable only for moderate epigastric tenderness. On blood work, CBC and electrolytes were normal, but amylase was elevated at 207 U/L, GGT 108 U/L. Other liver biochemistry was also normal. Troponin I was < 0.10.

Other investigations included a normal ECG with no ST changes and a normal abdominal X-ray with no free air

apparent. Abdominal CT was unremarkable. Pain resolved completely within several hours and the next day the serum amylase was 147.

The post-ERCP worsening of pain was most likely an acute aggravation of the patient's pancreatitis (i.e. post-ERCP pancreatitis) by instrumentation and manipulation around the papillary orifice. Unfortunately, this is the most common complication of ERCP, accounting for more than half of the complications of endoscopic sphincterotomy in two large series.[13] In a large series from North America, acute pancreatitis occurred post-ERCP in 127 of 2347 cases (5.4%). 5.0% of those cases were mild-moderate, defined by consensus as serum amylase at least 3 times normal at more than 24 hours after ERC, and requiring hospitalization for a further 2-10 days. The remaining 0.4% of the cases was graded as severe, which required hospitalization of more than 10 days, and resulted in the development of haemorrhagic pancreatitis, pseudocyst, or required intervention (percutaneous drainage or surgery). In this patient's situation, her post-ERCP pain resolved and she was discharged home without lasting sequelae.

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# A Case Based Analysis of the Risk Factors and Prevention of Suicidal Behaviour

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**Abstract**

Suicidal phenomena in the form of suicidal thoughts, attempts, and deliberate self-harm are common among adolescents. Suicide is one of the top causes of death among young people between the ages of 15 and 24 in a number of countries. The annual rates of suicide in children are 1 in 100,000 and 10 in 100,000 in adolescents. The most common method is overdose. A number of factors including stressful life events, concomitant psychiatric or substance abuse disorders, and lack of social supports have all been associated with suicidal behaviour in this population. This paper aims to address the various factors influencing suicidal behaviour in adolescents and will be centred on a case involving a 15-year-old female who overdosed in an attempt to commit suicide. The various factors that may have played a role in this event and the ways in which it could have been prevented will be explored.

## Case Synopsis

A 15-year-old Caucasian female was rushed to the Emergency Department by ambulance early one morning in an unconscious state. Her past medical history included an early diagnosis of epilepsy, which she controlled by taking carbamazepine (Tegretol) on a regular basis. She was otherwise healthy.

Based on reports from her mother, her daughter was a member of an upper class family consisting of her parents and her younger brother. Besides her parents being admittedly "overprotective", their overall family dynamic was described as being "stable and supportive." Further descriptions of the young girl revealed that she was a "bright young girl" who had always been an "A" student and heavily involved in extracurricular activities. However, since she had started high school a couple of months ago, her behaviour had drastically changed. She began spending time with a new group of friends, her grades dropped significantly and she became more rebellious towards her parents. There were a number of times in which she had been caught hoarding new articles of clothing that her mother suspected she had stolen. There were also reports of her recently breaking up with her boyfriend because he had been unfaithful to her. This took an emotional toll on her.

On the day prior to admission, the girl failed to return home from school to take her usual afternoon dose of carbamazepine. After arriving home later that evening, her mother discovered that she had stolen several clothing items from a local retail store. After the initial confrontation and disciplinary action by both her parents, the girl said, "Good night and I love you" to her parents.

On the day of admission, her mother had found her early in the morning lying in a pool of her own emesis. An unopened bottle of liquor, an empty bottle of carbamazepine and an empty bottle of Advil were found next to her body. It was estimated that she had ingested 30 tablets of carbamazepine and most of the contents of the bottle of Advil. In addition, a number of suicide notes had been discovered in her dresser. She was rushed to the Emergency Department and resuscitated. She was then consulted by the paediatric medical student. At this point she was still unconscious with non-reactive pupils. Upon further examination, she had superficial lacerations on her wrist and profanities written on both of her forearms. Her mother sat next to her holding her hand while she cooperated in providing a history.

The girl was then transferred to the paediatric ward until she was at her baseline neurological status and her carbamazepine levels were within normal range. She was subsequently transferred to the adolescent medicine ward where crisis intervention took place and she was placed under strict surveillance.

## The Role of Mental Illness in Influencing Suicidal Behaviour

Alcohol can induce a depressive state when it is used on a regular basis.[1] When adolescents become intrigued by the euphoric effects of alcohol, they are often unable to anticipate the post-use depressive state that it induces. Alcohol has also been found to increase the risk of suicidal behaviour in adolescents.[2] Thus, alcohol use in conjunction with adolescent issues such as relationship instability, peer pressure, insecurity, and familial conflicts can exacerbate or induce depression in adolescents that may already be genetically predisposed.

Various psychiatric disorders (most commonly depression) have been linked to suicidal behaviour. Over 90% of children or adolescents that commit suicide have an associated psychiatric or substance abuse disorder.[1,3] The issue of whether the patient in this case had a genetic underpinning was explored. She denied a family history of suicidal behaviour or any psychiatric conditions such as depression, bipo-

lar disorder, anxiety, or substance abuse. She confessed to abusing alcohol on a number of occasions, but the onset was not indicated. It was hypothesized that if she started abusing alcohol when she began high school then her recent change in behaviour may be explained. In addition, her alcohol abuse may have triggered the onset of depression, thus predisposing her to suicidal behaviour. Studies have identified that there are a greater proportion of psychiatric conditions associated with attempted suicide in comparison to suicidal ideation. Therefore, substance abuse likely had a role in the transition from suicidal ideation to a suicidal attempt.[3] Conduct disorder, anxiety disorders, psychotic disorders, and eating disorders have also been linked to suicidal behaviour.[3]

### Conflict as a Risk Factor for Suicidal Behaviour

Recent stressful events often referred to as "precipitating factors" can also trigger suicidal behaviour. Peer relationship problems which include rejection, humiliation and isolation, as well as family problems such as arguments, conflict, separation, and divorce have all been identified as precipitating factors in suicidal behaviour in children and adolescents.[1,2] The patient in this case had been experiencing familial conflicts as well as relationship problems. She was often in disagreement with her parents with regards to a number of issues, had stopped communicating with them, and was no longer affectionate towards them. Studies have found that family discord and diminished quality of familial relationships predispose adolescents to suicidal behaviour. In addition, the presence of sexual and physical abuse within families has a very strong influence.[3] The relationship difficulties she experienced involved distrust from her boyfriend as well as a former "supportive" friend. Adolescents need to feel supported and welcome, especially during times of strife, and without this relief from daily turmoil may seek extreme solutions such as alcohol abuse, deleterious behaviour, and suicide. Quality time, family cohesion, and good parental supervision are protective forces in preventing suicidal behaviour.[3]

### Poor School Performance as a Risk Factor for Suicidal Behaviour

Academic difficulties (including poor academic achievement and criticism from teachers) have also been identified as a precipitating factor for suicidal behaviour in children and adolescents.2 The patient had been a high achiever until she started high school, at which point she started failing courses and became truant. It was challenging to distinguish whether her interest in high academic achievement changed due to the influences of her new peer group or perhaps the advanced level of training was too difficult to grasp. Despite the uncertainty of the cause and effect nature of her poor academic achievement, it is known that poor school performance leads adolescents towards substance abuse and various destructive activities. Poor school performance can make adolescents believe they are unable to achieve their future aspirations and may cause them to doubt their intellectual capabilities. In addition, it may be an embarrassing topic to discuss, especially if friends are doing well academically. A positive school environment and high academic achievement are protective against suicidal behaviour.[3]

### Living with a Chronic Disease as a Risk Factor for Suicidal Behaviour

"Why me?" is a question often posed by adolescents suffering from chronic illness. Physical disability and both terminal and chronic medical illnesses are associated with suicidal ideation and suicidal behaviour in adolescents.[1,3] Studies have found an association between specific disease, such as diabetes and epilepsy, and suicidal behaviour.[3] Additionally, a strong correlation has been identified between epilepsy and depression in adolescents. Standards of beauty and social norms put a lot of pressure on adolescents and peers may not deem an adolescent with a chronic illness to be "normal". On top of social issues and school pressures, it is a difficult task to take on the extra burden of a chronic illness at such a delicate time in life. The patient in this case had to report home each day after school to take her medication while all her friends ventured to the local mall or recreation centre. In addition, the fear of seizing in front of other students made her uneasy and she was sure she would be seen as an "outcast." Patients with epilepsy perceive a stigma associated with having epilepsy resulting from fear of the illness itself, the implications of the illness, the social impact it has, and the associated loss of independence.[4] Therefore, the breakdown of the girl's social support network, alcohol use, poor school performance, and the burden of chronic illness may have played a role in contributing to her suicidal behaviour.

### Prevention of Suicidal Behaviour in Adolescents

Studies investigating the treatment of adolescent suicidal behaviour are few in number, however, there are certain risk factors that predispose this population to suicidal behaviour.[3] The case discussed introduced a number of factors that may have played a role in initiating suicidal behaviour in one particular adolescent. Alcohol use, conflict, poor school performance and living with a chronic illness are risk factors for suicidal behaviour in any adolescent.

The patient in this case was followed up by a crisis team on a regular basis as well as the medical student from the paediatric service during the course of her hospital stay. Although a thorough interview had been conducted, the history obtained from the patient seemed "superficial" in that the life she was leading was not depicted as distressful or conducive to the events that led to her admission. She often denied any feelings of dysphoria and described her suicidal behaviour as a mistake that she had not carefully thought through.

It is difficult to foresee suicidal behaviour, however, in hindsight there were points at which a medical professional could have intervened earlier to prevent the suicidal act from taking place. According to studies, suicide prevention in the primary setting is high in specificity but low in sensitivity.[3] In a survey of primary care physicians, it was determined that 77% routinely screen their adolescent patients for suicidal behaviour despite a frequency of 47% suicide attempts in adolescents in the previous year.[3] Although, there is no clear consensus on the best way to prevent suicide in adolescents, it is important to identify risk factors as tar-

gets for interventions. Suicide prevention tactics for physicians and medical students in specialties that deal with adolescents are provided below.

### The Medical Professional's Role in the Prevention of Substance Abuse and Poor School Performance in Adolescents

1. Routine alcohol screening using the CAGE questionnaire in a confidential and non-accusatory manner.
2. Private regular checkups with adolescents so that signs of abuse and various social aspects such as sexual activity, substance abuse, academic troubles and conflicts can be explored.
3. Drop the white coat. The more comfortable an adolescent is with their doctor, the more likely they will discuss confidential issues.
4. Using terminology that adolescents understand gives them the sense that no judgement is being passed, and that they should not feel inferior.
5. Referral to anonymous support groups for those involved in substance abuse or those with suicidal ideation or previous attempts.
6. Education on substance abuse, the short term and long term consequences, and tips on how to say "NO" should be available in pamphlet form from the office as well as through brief in-office counselling sessions.

### The Medical Professional's Role in Dealing with Familial Conflicts Experienced by Adolescents

Have occasional in-office meetings with the family to explore family dynamics and intervene on maladaptive patterns. The recognition of dysfunctional family dynamics can allow the physician to refer families for supportive counselling.

### The Medical Professional's Role in Dealing with Chronic Illness in Adolescents

1. Four main tactics can be utilized to make living with chronic illness easier for an adolescent:
2. Referring adolescents with chronic illnesses to support groups formed specifically for people experiencing chronic disease.
3. Ensuring that adolescents are well educated about their disease and various aspects such as incidence, prognosis, and course.
4. Prescribing medications that maximize compliance with infrequent dosing, easy administration, and easy incorporation into busy schedules.
5. In-office counselling on methods of coping with their illness and exploring what it is like for them to live with their illness.
6. Broadly, one can advocate for more local groups that deal specifically with a particular chronic disease such as epilepsy. For instance, Epilepsy Toronto is a support group currently available to children and adolescents living with seizure disorders and their families. The organization offers ongoing support groups for adults with epilepsy, parents of young adults with epilepsy, and surgery patients, and also offers employment services.[5]

### Conclusion

Adolescence is a time of transition, which is usually accompanied by numerous social and academic demands. These pressures often result in feelings of hopelessness and may ultimately lead to substance abuse, suicidal behaviour, and other destructive behaviours. This is a crucial time in which there is an increased need for social support networks in the form of supportive families, school counsellors, and teachers, as well as the support of the physicians who often see these individuals once a year at the most.

The case of the 15-year-old girl who overdosed in an attempt to end her life was beneficial in providing exposure to the various factors that influence suicidal behaviour in adolescents. The risk factors identified include alcohol use, social conflict, poor school performance, and chronic illness. It is evident that medical professionals have a role in intervening as early as possible and becoming advocates for this susceptible population by ensuring adequate follow up, in-office counselling, educational resources, as well as prompt referrals to various community services as needed.

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# Suicide in the Elderly

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**Abstract**

Suicide in the elderly is a serious public health issue worldwide. Seniors have to cope with a number of stressors, such as illness and social isolation, which predisposes them to self-harm. The factors that predispose seniors to suicidal behaviour are explored in the *Stress-Diathesis Model*. This model posits that certain unique personality factors and neurochemical abnormalities may leave individuals at greater risk of violent self-abuse. Recent neuroimaging and molecular studies by several authors have corroborated this theory. This model has been used to develop a multidisciplinary approach towards suicide prevention.

## Introduction

### The epidemiology of suicide in the elderly

Suicide is a significant and growing problem worldwide. In 2000, 815,000 people committed suicide globally, as compared to 520,000 homicides that year.[9] There is a bimodal distribution in the age groups most prone to suicide: youth aged 14 to 25 and seniors aged 65 and older. The Canadian suicide rate in the general population estimates 12 suicides per 100,000 people, while in seniors this rate increases to 30 per 100,000.[13] In 2003, there were 442 suicides in seniors 65 and older in Canada. The majority of this figure were males, with suicide rates in female seniors being as low as 9 per 100,000.[5]

Research has shown that seniors tend to have lower rates of suicidal ideation than youths. However, suicide attempts in seniors are more likely to be successful. This has been attributed to three factors:

- Use of highly lethal means for committing suicide: The most common modes used by seniors in Canada are firearms (28%) and hanging (24%).[5] As we shall see later, such violent and aggressive self-harm is associated with changes in critical neurochemical systems in the victims' brains.
- Seniors are more likely to live alone: This makes them less likely to be discovered in time after a suicide attempt.[5]
- Seniors are less healthy than other populations: This puts them at greater risk of dying as a direct result of the injury, and reduces their likelihood of survival after surgery or during hospitalization.[5]

### The Stress-Diathesis Model

Thus, suicide in the elderly is a significant public health issue in Canada. There are several risk factors and stressors in the elderly population that increases their risk of committing suicide[5]:

- Age: The number of suicides increases with age among seniors, with 90 year olds having a suicide rate as high as 45 per 100,000. These trends are reflected in the US data as well.
- Psychiatric Illness: Conwell *et al.* (2000) found that DSM IV axis I disorders are strongly associated with an increased risk of suicide. These include mood disorders (depression, bipolar), anxiety disorders, and psychotic disorders. The strongest increase in relative risk of suicide, however, is associated with major depressive disorder. Psychiatric illnesses are also associated with the use of more violent means of committing suicide.
- Other Chronic and Acute Illnesses: Many studies have shown an increased risk of suicide in elderly persons with non-psychiatric medical illnesses. For example, Juurlink et al. (2004) showed an increased relative risk of suicide with chronic illnesses such as congestive heart failure and chronic obstructive pulmonary disease. There is also an increased risk with neoplastic diseases such as breast cancer. Studies have demonstrated that the risk of suicide is also strongly associated with the degree of pain felt by the patient.[9] This means that diseases associated with severe chronic pain tend to have an increased risk of suicide.
- Social/Cultural Factors: The risk of suicide in the elderly varies across cultures, with a higher risk in North American and Western European societies.[5] In North America, studies have shown that family discord, financial difficulties, and relationship troubles are associated with an increased risk of suicide. Also, bereavement after the death of a spouse increases the risk. Social isolation and a lack of social interaction have also been linked to an increased risk of suicidal behaviour.[1]

In summary, there are a number of factors that, when compounded, put an elderly individual at risk of suicide. Adverse life events, chronic and acute illnesses, mental health issues, and social isolation combine to drive seniors to suicide each year. However, the above stressors are very common in our society, and most seniors who face them do not commit suicide. What differentiates a person who decides to end his/her life from another who does not? Experts in the field have advanced a theory called the Stress-Diathesis Model to explain this phenomenon.[10] This theory speculates that while many individuals may face Stressors like the ones outlined above, the individuals that do commit

suicide have certain Diatheses, or predispositions, toward suicidal behaviour. Scientists have theorized that a combination of a vulnerable personality type and certain neurochemical imbalances make some seniors more likely to commit suicide. These two factors are discussed in further detail below:

### Personality Traits

Several studies have shown that suicide victims have distinguished personality traits that put them at increased risk. For example, Duberstein *et al.* (1994) found higher scores for Neuroticism and lower scores for Openness to Experience (OTE) in suicidal seniors in a landmark case-control study. Harwood *et al.* (2001) showed that these individuals had an accentuation of anxious personality types. Hence, these individuals are less capable in handling social and psychological stressors. Their highly neurotic and low OTE personalities also make them less likely to seek help in times of great distress, and increase the likelihood of them escaping detection. When faced with such stressors, these individuals develop characteristically faulty cognitive schema, such as a negative outlook on themselves, and thus acquiring the self-image of a "loser".[5] Secondly, these seniors tend to believe that there is no escape from their current situation, and this feeling of helplessness may help to fuel their self-harming behaviours. Lastly, individuals also feel that there is no escape from their predicament and thus, are driven to self-harm as a result of their cognitive distortions.

### Neurochemical Abnormalities

The predisposition to suicide may also be reflected in a malfunctioning neurological circuitry in these individuals. Two major neurochemical systems have been implicated by relatively recent research in this area. These include the Serotonergic system and the Hypothalamo-Pituitary-Adrenal (HPA) Axis.

For several years, researchers have known that the cerebrospinal fluid (CSF) of suicide victims contains lower levels of a serotonin metabolite, 5-HIAA.[10] Recent studies have demonstrated that the level of TPH, an enzyme involved in serotonin synthesis, is reduced in the brains of suicide victims.8 Moreover, autopsy and neuroimaging studies have shown lowered levels of the serotonin transporter protein in presynaptic neurons and in several areas of the brain including the ventro-medial prefrontal cortex.[6,9] Therefore, there appears to be a reduced synthesis of serotonin in key areas of the "suicide brain". Significantly, this effect has been found to be independent of psychiatric diagnoses such as major depressive disorder.[5] There is a compensatory increase in the postsynaptic serotonin receptors (5-HT1a and 5-HT2) in response to this, in the same areas of the brain. The ventromedial prefrontal cortex is involved in inhibition of behavioural and cognitive impulses.11 Thus, hypofunction of this area is theorized to lead to disinhibition of aggressive behaviour, leading to aggressive and violent self-harm.

Similarly, the HPA axis has also been found to be malfunctioning in suicidal patients. Studies have demonstrated HPA axis overactivation in the brains of suicide victims.[8] This has been demonstrated via dexamethasone-suppression tests, where higher levels of cortisol are found in suicidal patients, indicating a lack of suppression of the HPA axis. While HPA axis overactivation is associated with depression and other affective disorders, newer studies have demonstrated that, in some individuals, there is a mild chronic HPA overactivation.[5] Thus, HPA overactivation is now considered a trait-dependent factor rather than a state-dependent one. Interestingly, neuroimaging studies point to reduced CRF receptor concentrations in the prefrontal cortex, the same brain area associated with serotonergic malfunction.[8] In fact, the serotonin system and the HPA axis are theorized to be interacting with each other. For example, stress and cortisol overexpression may lead to reduced serotonin release via cortisol-mediated inhibition of serotonin synthesis.[8] Thus, authors have theorized that individuals with a mildly hyperactive HPA system are more susceptible to serotonergic malfunction when faced with stressful situations.[8] In addition, persons who already have an altered serotonin metabolism may be highly vulnerable to stressors that activate the HPA system and impair serotonin release.

Interestingly, both the serotonin and HPA systems may be affected by genetic and environmental influences. Animal studies have shown that human-raised monkeys have lower levels of serotonin than monkeys raised by their mothers.[11] These levels persist into adulthood. Similarly, victims of child abuse have overactive HPA systems according to some studies. Thus, early life events may alter these critical neurochemical systems to increase one's susceptibility to suicidal behaviour later on in life.

Suicide and suicidal behaviour also has a strong familial preponderance. Studies have shown that people who commit suicide often have a positive family history of suicide attempts.[5] Also, suicide rates in monozygotic twins are higher than those in dizygotic twins. Thus, along with environmental stressors, there is good evidence to support a genetic predisposition to suicidal behaviour. Research to identify candidate genes to explain this association is currently underway.[6] Several candidate genes have been explored so far (e.g. TPH, 5HT1a, 5HT2a) but to date, no convincing evidence has been found to link a particular polymorphism of these genes to increased suicidality. This is one of the new frontiers of suicide research, since being able to predict one's risk for suicide may allow early intervention and better outcomes.

Neuroanatomical studies are another area of cutting edge research in the field of suicide research. For example, Siever *et al.* (1999) have shown that a reduced response of the prefrontal cortex to fenfluramine (a drug that increases serotonin concentrations) is associated with suicide risk. Positron Emission Tomography studies have been used to confirm the belief that the prefrontal cortex inhibits the emotional drive from the amygdala.[11] Thus, hypofunction of the prefrontal cortex may then trigger disinhibition of the emotional drive from the amygdala, leading to violent self-harm.

### Conclusion and Strategies for suicide prevention

Elderly suicide is a complex and multidimensional public health problem. Seniors face a number of stressors in their

lives, including chronic illness, depression, and pain. They also face a number of social stressors such as isolation, financial problems, and relationship difficulties. As shown by the stress-diathesis model, these stressors affect certain vulnerable individuals with particular severity. These are individuals with certain personality traits, prone to a rigid and inflexible outlook and high degrees of neuroticism. In addition, newer research has shown that neurobiological changes, such as hypofunction of the serotonin system and overactivity of the stress axis, may predispose individuals to self-harm. This model helps to explain the high rates of elderly suicide and why some individuals are more prone to mistreating themselves, despite facing the same conditions as many other seniors. This model is a work in progress, however, since many of the studies on neurochemical imbalances rely on associations rather than establishing definite causal pathways. The genetic basis of suicide risk has also yet to be established. This model does, however, provide a good framework to guide our hypotheses on the causes of suicide in the elderly. The Stress-Diathesis Model also provides an excellent platform for the development and improvement of suicide prevention strategies. The stressors and diatheses identified above can be addressed via a multidisciplinary approach focusing on primary prevention as well as pharmacological therapies to correct neurochemical imbalances. Some of these approaches are outlined below[5]:

- Better training of Health Care Providers (HCPs) to recognize the signs and symptoms of suicidal ideation in the elderly. This is important because the elderly often present with non-specific signs and symptoms overlying a major issue. This approach has been shown to reduce suicide rates in one case-control study.[8]
- Some locations have initiated social programs to reduce the isolation felt by seniors. These include friendly visiting by volunteers who provide seniors with much needed social interaction, as well as awareness programs in the general public.
- Legislation has been passed in several countries to limit access to means of committing suicide. This includes gun-control legislation in Canada and the US, where shooting is a common mechanism of suicide. In the UK, legislation has been passed to control access to paracetamol, which is a drug that can lead to life threatening complications after an overdose.[5]

As a result of breakthroughs in the neuroscience behind suicide, newer drugs are being developed to selectively target serotonin receptors (e.g. only the 5HT1a receptors). These drugs, together with psychotherapy, lead to improved outcomes for seniors and demonstrate the benefits of conducting research in this area.[11]

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# The Role of Prophylactic Antiviral Therapy in Pregnant Women Infected with HSV-2

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**Abstract**

Pregnant women infected with Herpes Simplex Virus Type 2 (HSV-2) are commonly encountered in obstetrics. The prevalence of both genital herpes and neonatal herpes is on the rise. Due to the devastating nature of neonatal HSV infection, it is important for physicians to prevent the acquisition of HSV-2 in pregnancy by educating pregnant women about the associated risks as well as recognizing and treating genital herpes outbreaks promptly. However, there has been no clear consensus on the role of antiviral therapy during pregnancy. The objectives of this paper are to determine the role of antiviral therapy in preventing and treating Genital Herpes outbreaks during pregnancy and to develop an algorithm for use in obstetrical practice. Based on recent literature, acyclovir therapy after 36 weeks gestation can be considered in women who have had a primary case of HSV-2 during pregnancy or who have had recurrent genital herpes during pregnancy to decrease viral shedding, outbreak incidence and caesarean section rates. No neonatal complications above baseline have been identified in mothers who receive antiviral therapy during pregnancy. However, too few studies have been done to exclude the possibility of harm to the fetus in the long term and there is no clear consensus on the management of latent or infrequent disease or on the use of antiviral therapy before 36 weeks gestation. An algorithm has been developed for use in obstetrics that incorporates HSV-2 screening, patient education, antiviral therapy and the freedom of choice in the management of HSV-2 during pregnancy.

## Case Scenario

A young pregnant woman visits the antenatal clinic for her first prenatal visit. She has been diagnosed recently with HSV-2 and is worried about transmitting the virus to her baby. She has heard about various drugs on the market that can be used in infected pregnant women. What role does antiviral therapy have in preventing and treating genital herpes outbreaks during pregnancy and what are the risks of antiviral therapy in pregnancy?

## Introduction

Approximately 22% of pregnant women are seropositive for HSV-2 and approximately 2% acquire genital herpes during pregnancy.[1] Genital herpes can present in a variety of ways ranging from asymptomatic or minimal lesions to widespread genital lesions with severe local pain, dysuria, sacral paresthesia, lymphadenopathy, fever, malaise and headache. Rarely, aseptic meningitis or disseminated disease may occur. Newly acquired infections are most likely to present with severe symptoms whereas reactivation disease is more commonly mild. Detection of HSV-2 can be done by culturing vaginal secretions or by the more sensitive polymerase chain reaction (PCR) of vaginal secretions. Antibodies to HSV develop in 6-12 weeks post-infection and can be detected by type-specific serologic assays.

An outbreak of genital herpes during pregnancy is worrisome if it occurs close to the time of delivery, mainly due to the possibility of vertical transmission. Neonatal HSV occurs in about 1 in 3,200 live births.[1] The chance of intrauterine transmission is extremely rare and occurs mostly in cases of primary outbreaks during pregnancy. The most important risk factor for transmission to the neonate is contact with infectious maternal secretions during vaginal delivery. This occurs mostly in women who have acquired a primary infection during the final trimester of their pregnancy and makes up 60-80% of neonatal herpes cases.[1] These mothers are at high risk of vertical transmission because they have not yet developed antibodies and therefore have higher viral titres than those who have been infected for longer periods of time. At the time of delivery, there is a 30-50% risk of neonatal herpes infection if asymptomatic shedding of the virus occurs. This risk is much greater than for women who have symptomatic reactivation at the time of delivery (3% risk of neonatal herpes).[1] (Table 1)

| Stage | Vertical Transmission Rate |
|---|---|
| Primary asymptomatic shedding in HSV-2 acquired after third trimester | 30-50% |
| Symptomatic reactivation | 2-3% |

**Table 1**. Vertical transmission rates based on stage of infection

Neonatal Herpes is defined as "the diagnosis of an HSV infection in an infant within the first 28 days of life".[1] Forty five percent of cases present with ophthalmic, oral and dermatologic findings without involvement of major organs. The most severe complications arise in central nervous system (CNS) disease and disseminated herpes. CNS involvement occurs in one third of cases and is characterized by irritability, lethargy, seizures, tremors, poor feeding, temperature instability, and bulging fontanelles. Disseminated HSV, which occurs in 25% of the cases, involves multiple organs and can be fatal even if the neonate is treated. Mortality in disseminated and CNS HSV occurs in 30% of neonates , while 40% of survivors are left with severe neurological impairment. It is therefore important to

diagnose and manage genital herpes during pregnancy to prevent neonatal transmission and the associated complications.

### Antiviral Therapy in Pregnant women with HSV-2

Currently, the standard of care is to perform a caesarean section in any woman with active genital lesions or prodromal symptoms at the time of labour.[1] The 2001 National Guideline for the management of genital herpes (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Disease) recommends continuous acyclovir therapy during the last month of pregnancy in women with severe or frequent recurrent genital herpes. The American College of Obstetricians and Gynecologists (ACOG) also supports this recommendation. The American College also recommends treatment of Primary HSV at any stage of pregnancy with a 7 to 14 day course of an antiviral agent.

There are currently three main antiviral drugs available for treatment of HSV-2 in non-pregnant women. These are Acyclovir, Valacyclovir and Famciclovir. Acyclovir and Valacyclovir have both been tested in pregnant women, however the majority of these studies involve only Acyclovir. Acyclovir is a nucleoside analog that is highly specific for HSV infected cells.[1] Once Acyclovir enters the infected cell it is activated by the viral thymidine kinase and is then capable of inactivating viral replication. Valacyclovir has the same mechanism of action as Acyclovir with the exception that Valacyclovir has greater gastrointestinal availability and greater conversion to its active metabolite in the blood stream. Valacyclovir's higher bioavailability decreases the dosage required and thus may improve patient compliance. Smaller studies have concluded that Valacyclovir is equally as effective as Acyclovir in suppressing episodes of recurrent genital herpes.[1] Famciclovir has the same mechanism and also has greater bioavailability than Acyclovir. However, no studies address its use in pregnancy and therefore it is not recommended. Currently, Acyclovir, Valacyclovir and Famciclovir are pregnancy category B drugs as per the Food and Drug Administration (FDA) (no evidence of risk in humans, but there are no controlled human studies). Table 2 shows the recommended doses of antiviral medication for herpes in pregnant women.

| Indication | Dosage and Duration |
|---|---|
| Primary or first-episode HSV-2 | Acyclovir 400 mg po tid for 5 days or Valacyclovir 500 mg po bid for 5 days |
| HSV Symptomatic recurrent | Acyclovir 400 mg po tid for 5 days or Valacyclovir 500 mg po bid for 5 days |
| Daily suppressive therapy | Acyclovir 400 mg po tid from 36 wk GA to delivery or Valacyclovir 500 mg po bid from 36 weeks gestational age (GA) to delivery |
| Disseminated HSV or other severe, rare manifestations | IV acyclovir |

**Table 2.** Recommended Doses of Antiviral Medication for Herpes in Pregnancy

### Studies examining the use of antiviral therapy in pregnant women with HSV-2

A number of studies have investigated the role of antiviral therapy in pregnancy.

Sheffield *et al* (2006) conducted a randomized clinical trial involving women at 36 weeks gestation, 170 women of whom were treated with Valacyclovir while 168 were treated with placebo. The sample consisted of 82% of women who had recurrent genital herpes, 12% who had a first episode during pregnancy but had acquired HSV-2 in the past and 6% who had a first primary episode. Infants were followed up for neonatal complications. Four percent of the Valacyclovir group had recurrent genital herpes requiring caesarean section in comparison to 13% of placebo group (P=.009). Two percent of the Valacyclovir group had HSV detectible by culture in comparison to 24% in the placebo group (P=0.02). No infants had neonatal HSV. There were no differences in neonatal or obstetric complications between the two groups.[2]

Andrews et al (2006) conducted a study involving HSV-2 seropositive pregnant women with similar recurrence histories. Fifty-seven women were treated with Valayclovir and 55 with placebo. Approximately 10% of HSV recurrences occurred in the Valacyclovir-treated group in comparison to 27.3% in the placebo group (P=0.023). The authors concluded that Valacyclovir is useful for decreasing the incidence of HSV recurrence during the time period of treatment. No neonates had symptomatic HSV infection before discharge from hospital or up to two weeks post partum.[4]

A study by Watts et al (2003) was one of the largest randomized masked trials to evaluate Acyclovir prophylaxis at 36 weeks gestation. Seventy-eight women received placebo and 84 women were assigned to the Acyclovir group. HSV cultures and PCR positivity were 34% in the placebo group and 7% in the Acyclovir group (P=0.03). Overall, this study concluded that Acyclovir prophylaxis at 36 weeks reduces the risk of symptomatic HSV recurrence at delivery and thus leads to a decrease in caesarean deliveries. No statistically significant differences in neonatal outcomes were seen between the study groups.[3]

In summary, either Acyclovir or Valacyclovir therapy after 36 weeks gestation should be considered in women who have had a primary case of HSV-2 during pregnancy or who have had recurrent HSV during pregnancy to decrease viral shedding, outbreak incidence and caesarean section rates. Since asymptomatic shedding during the time of delivery is the most likely mode of transmission to the fetus, the prophylaxis is administered whether the mothers are symptomatic after the outbreak or not. Outbreaks that occur prior to 36 weeks gestation should be treated with a 7 to 14-day course of Acyclovir solely for relief of maternal symptoms because evidence has not shown antiviral therapy to decrease intrauterine transmission to the fetus. In women with HSV-2 who have latent disease, the usefulness of prophylactic antiviral therapy is less clear.

### Safety of Antiviral Therapy in Pregnancy

Acyclovir crosses the placenta and is excreted by the fetal kidneys. It can be found in the amniotic fluid and fetal tissues.[1] Registries of neonates who have been exposed to Acyclovir *in utero* have not identified significant teratogenic effects. In addition, studies have not addressed the risk of rare or long term complications. Most of the concern with antiviral use in pregnancy stems from Acyclovir toxicity data in neonates with HSV. Neutropenia and renal insufficiency have been identified as possible complications.[1] Therefore, these are potential complications that the neonate in utero may face and should be discussed with all pregnant women before initiating antiviral therapy. Sheffield et al found no cases of neutropenia or significant anemia in neonates exposed to Valacyclovir *in utero.* There were no adverse hepatic or renal effects.[2] Fortunately, large-scale studies on Acyclovir and small-scale studies on Valacyclovir have not

shown any adverse effects in pregnant women in comparison to placebo groups.[5] However, the studies are limited in the following ways:

- Too few studies done on the long-term effects and rare outcomes of antiviral agents on children
- No studies done on the safety of antiviral drugs before 36 weeks gestation
- No studies done on the safety of Famcyclovir in pregnancy
- The role of antiviral prophylaxis in those with latent disease or a history of infrequent outbreaks has not been defined.

### An algorithm for pregnant women with HSV-2

Based on the literature and current guidelines an algorithm has been developed for possible use in obstetrics:

1. Incorporate two-stage HSV-2 serology testing into the prenatal assessment. First stage at first prenatal visit to allow for early identification, prevention of transmission to partner and preparation for delivery. Second stage at 24-28 weeks gestation (at time of gestation diabetes screen) to identify new sub-clinical infections with the potential for viral shedding during time of delivery.
   a) If screen positive, perform detailed inquiry on frequency and severity of attacks
   b) If screen negative, implement prevention tactics:
      Voluntary HSV-2 serology of partners; if declined, the promote condom use
      Education on condom use, neonatal herpes, and genital herpes symptoms
2. Monitor for the signs of HSV-2 outbreak at each visit:
   - Mild disease: minimal lesions and mild discomfort
   - Severe disease: widespread genital lesions and severe local pain, dysuria, sacral paresthesia, tender regional lymph node enlargement, fever, malaise and headache
   - Aseptic meningitis
   - Disseminated HSV: flu-like prodrome including fever that progresses to pneumonitis, hepatitis, and/or encephalitis, with or without characteristic skin lesions after mid-pregnancy.
3. Treat all primary outbreaks regardless of trimester with acyclovir due to low, but potential risk of intrauterine transmission and for maternal symptomatic relief. Explain the benefits and uncertainty of treatment. No studies have investigated risks of antiviral use early in pregnancy. This practice should be optional as it is mainly for maternal symptomatic relief.
4. Initiate Acyclovir prophylaxis at 36 weeks gestation in mothers with a history of frequent or severe outbreaks prior to pregnancy. The role of prophylaxis in this case is to decrease viral shedding at time of delivery and therefore allow for a vaginal delivery to take place. There is a low risk of transmission in reactivation disease.
5. Inquire about HSV symptoms and perform a thorough examination of the cervix, vagina, and vulva at time of admission in labour.
6. Perform a Caesarean delivery in all women with active lesions at time of labour.
7. Offer vaginal delivery in women with latent or mild reactivation disease who have no active lesions at time of delivery or those who have been treated with acyclovir prophylaxis due to the low vertical transmission rates. If lesions are discovered then proceed to caesarean section. In such cases, avoid artificial rupture of membranes, fetal scalp electrodes, and vacuum or forceps delivery due to the increased chance of HSV-2 transmission.
8. For neonates born to women with active HSV-2 lesions, follow up with neonatal type-specific glycoprotein G based serologic testing at birth and again in 12 weeks to allow time for the development of antibodies if not present at birth.

There is currently no clear consensus with regard to HSV screening as a component of routine antenatal screening. One concern with this intervention is its cost effectiveness. Baker et al (2004) examined this issue by using a decision analysis approach. They concluded that the decrease in neonatal herpes and in caesarean section rates seen with screening and prophylaxis suggest that this could be a cost-effective practice.[7] However, more studies are needed to address seropositive individuals without a history of herpes outbreaks. Thung et al (2005) found that HSV-1 and HSV-2 screening and antiviral prophylaxis were not cost effective practices. They do make the point that these studies are based on the population at large and it is important to address individual women on a case-by-case basis.[6]

### Conclusion

HSV-2 infection is prevalent among pregnant women and the infection rate is currently on the rise. The main concern with HSV-2 in pregnancy is the risk of vertical transmission to the neonate and the subsequent development of neonatal herpes. Although the prevalence of neonatal herpes is low, it has a devastating impact on neonates and is associated with high morbidity and mortality. Therefore, HSV-2 in pregnancy is an important health concern. HSV-2 is both treatable and preventable with appropriate screening, counseling and management. The literature supports the use of antiviral agents such as Acyclovir and Valacyclovir at 36 weeks gestation for prophylaxis against HSV-2 recurrence at the time of delivery in woman who have frequent recurrences or who have acquired HSV-2 during the pregnancy. However, the indication for antiviral prophylaxis in latent or infrequent disease is less clear and the long-term risks have not been well studied. Therefore, there is a clear need for more studies to be done on the role of antiviral therapy in pregnancy. However, an algorithm has been proposed which takes into consideration the current guidelines with regard to the management of HSV-2 in pregnancy and as well as advances in recent literature. The algorithm involves HSV prenatal screening, various precautionary measures and options to consider in an attempt to decrease vertical transmission. It also promotes patient choice and awareness and may increase vigilance in surveillance of HSV-2 among physicians. As the associated neonatal morbidity and mortality is high, it is important to try to prevent acquisition of HSV-2 in pregnancy by educating pregnant women about the risks, screening for genital herpes in high-risk individuals, and recognizing and treating genital herpes outbreaks promptly. Through prenatal screening, education and treatment, both maternal and neonatal complications from HSV can be reduced.

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# Health Information Technology: Landscape and Directions

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**Abstract**

Health information technology (HIT) is a rapidly advancing field that promises to reduce costs, streamline healthcare delivery, and empower patients to make informed healthcare decisions. The technologies that are currently being integrated are diverse, ranging from hospital-based electronic medical records to clinical decision support systems. Efforts are underway to ensure that various healthcare stakeholders can share healthcare data and interact with other related HIT systems, rather than generating volumes of data in a silo. Once healthcare data is secure and interoperable between different stakeholders, a new world of applications will be possible that allows for real-time data analysis. This will lead to continuous quality improvement, an increased education for patients, and their involvement in the healthcare decision-making process. Although the introduction of HIT systems has not always been smooth, the future is promising as long as government, administration, and industry continue working together to move healthcare into the 21st century.

Health information technology (HIT) is viewed by many stakeholders as a potential saviour for the healthcare industry. It is widely believed that effective use of HIT will reduce costs (allowing administrative costs to be transferred directly towards patient-care), streamline healthcare delivery, reduce redundancies, empower and enable patients to make more informed decisions, and ultimately improve healthcare outcomes. Given the tremendous power that information technology (IT) has shown by drastically eliminating inefficiencies in the financial, tourism, business, sales, real-estate, and entertainment industries, the relatively slow integration of IT into healthcare means patient care is less equitable and less ideal than it could be. Numerous recent studies have supported this claim.[1] Furthermore, the delayed introduction of HIT harms patients at individual and population levels. Individual patients are harmed when physicians make diagnoses or treatment decisions without the most complete and accurate history available. The population's health is ill-served when limited healthcare funds are being spent on a redundant, inefficient system that could otherwise be diverted to improved patient care or new health research.

HIT is not yet a well-defined entity; numerous authors have chosen to define and categorize the various technologies within healthcare using different models.[2,3] Semantics notwithstanding, several of the most important technological advances that are now becoming integrated into our model of healthcare delivery are described below.

### Computer Practitioner Order Entry (CPOE)

CPOE ensures that orders (medication, tests, procedures, etc.) are complete and legible while providing logic to flag contraindications and raise warnings. CPOE has been proven to reduce preventable adverse events.[4] Electronic message sending between departments and organizations makes message delivery more efficient and less prone to error.

### Computer-assisted Decision Support (CDS)

CDS brings the latest evidence-based medicine (EBM) research and guidelines directly to physicians in the hospital and clinics. CDS assists with diagnosis, treatment, and follow-up and ensures that the current best-practices are available and accessible to all patients. As an extension, patients can be monitored and physicians can be alerted to status changes, thereby facilitating quick decision-making. CDS also serves as a way to measure practices against standard industry guidelines, and thus facilitating quality improvement efforts.

### Telehealth

Telehealth is the use of telecommunication technologies in healthcare delivery. The use of email, digital imaging and video, voice-over-IP, and robots are enabling new opportunities for the delivery of holistic care. Videoconference specialist consultations, email-visits using digital images, remotely monitored home-dialysis, and the use of robots to perform remote surgeries are all examples of the expanding ability of the healthcare system to reach patients.

### Electronic Health Records (EHR)

In the broadest sense, an EHR is the complete patient health history from hospital records, patient charts, pharmacy records, insurance company records, lab records, and the patient's own recollection – stored securely and electronically.

Hospitals are introducing electronic medical record (EMR) systems that generate volumes of patient data. Imaging and lab results are all stored in separate databases. Governments, pharmacies, and insurance companies store patient data including diagnoses, medication, and treatment codes. Some patients have started storing their family's medical history on personal computers or Internet health portals. Grouped together, this information has the potential to transform how we deliver healthcare.

### Healthcare IT Network

Efforts are underway to ensure that various healthcare

stakeholders and systems can communicate with each another in a secure and timely fashion while respecting patients' privacy. Interoperable electronic health records are the holy grail of HIT. Interoperability ensures that health records are portable and transferable between healthcare facilities. It also allows stakeholders to develop applications that use these records to present useful, contextual, timely information to patients and healthcare workers.

In addition to the benefits of electronic health records, an integrated health network provides a means to monitor epidemiological trends and study outcomes. For instance, it can be used as a bio-surveillance mechanism to quickly identify disease outbreaks. This new, rich source of data can help in the continuous improvement of healthcare by quickly identifying the best practices and implementing structures and processes that align with those ideals.

The Canada Health Infoway (http:// infoway-inforoute.ca) is spearheading efforts to make sure that HIT initiatives are interoperable and accessible to all Canadians. In the United Sates, various governmental departments, private companies, hospital networks, and insurance companies are working together and individually to create interoperable health networks. Connecting for Health (http://connectingforhealth.org) is one example of public-private collaboration consisting of over 100 organizations attempting to develop a common HIT platform.

## Personal Health Records (PHR) and Health Portals

Very closely related to the notion of EHR is the personal health record. PHRs are the subset of EHRs that are stored, controlled, and accessible by individual patients. They can include data from hospitals, outpatient clinics, insurance companies, pharmacies, real-time health monitoring devices, and self-entered data. By having ownership over the data, the patient is in control of who is able to view the data and how it is used.

**Storing Health Information in a PHR**

- Past test results and/or baseline measurements (i.e. lab tests, blood work, imaging, genetic testing)
- Immunization records
- Medication history
- Reactions to medications
- Hospitalisations
- Dates of major acute health events
- Family health history
- Allergies
- Past physician contact information
- Developmental milestones
- Previous diagnoses, discharge summaries

PHRs can empower patients by allowing them access, control and decision-making power over their personal health data. This is important as patients who are educated about their health and more involved in the decision-making process are more likely to be adherent to medication instructions and to follow routine screening schedules.[5]

Personal health portals encompass PHRs and the network of applications and abilities that PHRs enable. For example, a website that has access to a family's health information can help the family schedule appointments, manage medications, research diseases, find local specialists, discover new therapeutic options, and connect with local support groups. It can offer teaching guides about the interpretation of lab results, suggest healthy diets, propose questions to ask physicians, and help the family set realistic health and wellness goals. In the future, a health portal may serve as a hub where patients can conduct e-visits for routine care.

PHRs and health portals are among the most intriguing and rapidly growing areas of HIT. In the United States, insurance companies, hospitals, pharmacy networks, and privately-held technology companies are all competing and collaborating to provide patients with PHR solutions because of the tremendous opportunities they hold to empower patients and alter healthcare delivery.

## Patient Empowerment

One of the more significant attributes of PHRs will be their ability to educate and empower patients, and make them informed consumers in an increasingly complex healthcare system. In Canada, primary care physicians are generally viewed as the managers of patients' health. However, given current healthcare constraints, it is nearly impossible for primary care physicians to be responsible for all of the following:

- Diagnose and treat
- Follow and integrate all the latest EBM guidelines
- Educate patients about:
  - Their condition
  - Various treatment options
  - How to take their drugs and why they are important
  - Screening reminders
  - Preventative measures
  - Lifestyle issues
- Integrate records and knowledge from specialist visits, lab results, and visits to other healthcare professionals such as chiropractors, dentists, and pharmacists
- Provide access to community healthcare resources
- Use primary preventative measures
- Promote health in the community
- Motivate
- Counsel
- Advocate

That is, however, what is currently expected of them. Clearly, patients who are educated and empowered to navigate the healthcare system can access better care than those who do not understand how the healthcare system works.

Additionally, there is an entire population of people who are reluctant to utilize the services of primary care physicians for reasons of language, culture, distance, inconvenience, lack of knowledge, or lack of availability. This population, which likely includes many at-risk individuals, can benefit by having access to tools and information that will help them make informed healthcare decisions.

Today, even when patients are motivated to take control of their healthcare, they do not always have adequate access to their health records to make informed decisions. Patients are not provided with the tools or information necessary to control their health decision-making. PHRs and health portals promise to open an exciting new world in which full and com-

plete medical histories, EBM, and patient-choice intersect to provide equity in healthcare and improved health outcomes.

## Challenges

While the use of HIT to improve outcomes is obvious to some, and has been backed by numerous studies, there is also evidence that inappropriate disruptive changes can have a negative impact on patient care. A paediatric health care facility may have experienced an increase in mortality after the installation of a CPOE system that required healthcare workers to spend more time at the computer and less time with patients.[6] More recently, it has been reported that Kaiser Permanente's effort to computerize medical records in California has led to numerous technical problems leading to sometimes inaccessible records and delays in patient care. Anecdotally, many healthcare workers complain that the increased documentation times associated with EMR systems give them less time to spend with patients.

Evidently, EHR software is in its infancy and still has room for improvement. It is also clear that local practices of healthcare workers must be taken into account so that they do not view HIT as an increasing work-burden without witnessing direct benefits. Successful software requires minimal changes to the workflow of current hospital staff, but still provides them with access to information more quickly and more completely than they would have had otherwise.

One such successful hospital software system, called Azyxxi, was designed by physicians in Washington D.C.'s Medstar hospital network. Azyxxi was not the product of a large budget, wide-scale rollout, and re-training of hospital staff. Instead, it was developed incrementally in-house, and initially deployed on only one hospital computer. However, because Azyxxi offered features demanded by staff that simplified their jobs and made information lookup exponentially quicker, it spread through the entire network of hospitals as more people used it and more information was fed into its database. Azyxxi is currently owned by Microsoft and will be deployed in the near future at John Hopkins Hospital and New York-Presbyterian Hospital.

Another positive development in healthcare IT is the collaboration between Intel and Motion Computing that resulted in a new type of device, the clinical mobile assistant (CMA). The CMA was designed to work within current hospital workflows. Its integrated hardware and customized software focused on enhancing patient safety, reducing medication dispensing errors, and easing staff workloads. Features such as a durable casing, an integrated camera, and barcode scanning are the results of countless hours of direct collaboration with nurses and clinicians.

## Future

While the technology currently exists to use HIT to improve healthcare delivery, its adoption remains slow and measured compared to the adoption of IT in other industries. Like many innovations in healthcare, politics and funding structures sometimes act to maintain the status quo. While it is clearly necessary to create a secure, interoperable IT infrastructure, motivate all stakeholders to share health data, and invest in applications that will make use of EBM, it is not clear how the funding or motivation will come together. Provincial Ministries of health and hospital administrators must work together to invest in long-term, interoperable solutions.

Today, implementation costs for many HIT solutions fall on individual clinics and doctors, even though they do not receive direct financial remuneration for improved healthcare outcomes. In the United States, the situation is even more complex; many healthcare stakeholders are able to profit from inefficient and redundant healthcare delivery and are hesitant to share medical data that might give other stakeholders competitive advantages. Clearly, changes to healthcare funding must reward innovation, quality, and long-term health outcomes at the expense of fee-for-service compensation.

Just a few years ago, the financial barriers, political barriers, lack of interoperability between healthcare systems, culture stigma against the use of IT in healthcare, and the general inertia of the healthcare industry against drastic changes would have made the widespread acceptance of HIT virtually impossible. The landscape, however, is changing. Everyone, including patients, physicians, and the government, is demanding more transparency and more accountability in healthcare. Policy-makers seem more inclined to find new and innovative solutions to help reduce costs and increase quality. Political pressure to encourage cooperation among healthcare stakeholders, public demands for increased choice and transparency, redefining of government healthcare priorities, and reward incentives that encourage private research and innovation are some of the keys to ensuring that systems are created to empower patients and ultimately make healthcare more equitable and patient-centered.

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# Survivin – A New Molecular Player in Head and Neck Cancer: Diagnostic, Prognostic and Therapeutic Implications

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## Background

Head and neck squamous cell carcinoma (HNSCC) constitutes the sixth most common type of cancer and accounts for 5% of all adult cancers worldwide. Despite modern therapies with reconstructive surgery and adjuvant or neo-adjuvant chemo-radiative modalities, the overall 5 year survival statistics have not significantly improved in nearly a quarter century.[1] The clinical behavior of HNSCC is difficult to predict based on classical histopathological parameters alone and therefore biological markers that can identify tumors with a more aggressive phenotype would be valuable to the oncologist in tailoring individualized management strategies.

Pathogenically, the development of HNSCC tumours has been associated with the mutagenic role of carcinogens which can induce specific mutations in different genes. This strong association thereby suggests a disruption in the cellular response to genotoxic damage. Apoptosis (programmed cell death) is a crucial biological process that prevents uncontrolled cell proliferation and eliminates harmful cells. Cells harboring multiple genetic alterations are normally eliminated by apoptosis and resistance to apoptotic stimuli has been shown to have a profound effect on tumorigenesis and the progression of malignancies.

Several proteins that inhibit apoptosis have been identified including the Bcl-2 family and the family of Inhibitor of Apoptosis Proteins (IAPs). IAPs are a group of structurally related proteins that are differentially over expressed in many cases of human malignant tissues to directly, or indirectly, inhibit activated caspases. While the molecular pathways of tumorigenesis are still poorly understood, in the last decade, the IAP Survivin has garnered some attention for its role in HNSCC.

## Survivin

Survivin is a single-copy gene located at 3% of the distance from the telomere on chromosome 17 (17q25). The gene is structurally unique among mammalian IAPs as it only contains a single Baculovirus IAP repeat (BIR) and lacks the COOH-terminal Really Interesting New Gene (RING) finger domain. More significantly, Survivin is uniquely expressed in normal human embryonal and fetal development and has been reported to be poorly expressed in normal adult tissues. Survivin expression does, however, become prominent in fast-growing cells such as transformed cell lines and human cancers.[2] In various malignancies, over expression of Survivin has been correlated with lower apoptotic activity. After sustaining unrepaired nuclear damage, this failure to undergo apoptosis can lead to enhanced mutation and genomic instability; a general characteristic of cancer progression.

Survivin is the only apoptosis inhibitor that is expressed in a cell-cycle dependent manner in the $G_2$ and M phases. Both amplification of the Survivin locus on Chromosome 17 and DNA demethylation in its promoter region have been reported as possible mechanisms of Survivin up-regulation in some cancers.[3] This epigenetic mechanism was suggested when it was found that DMBA (a potent chemical carcinogen) contributed to the promoter hypo-methylation of Survivin in chemically induced hamster buccal-pouch carcinoma cells.[4] Tanaka *et al.* soon confirmed these findings in a study of human oral squamous cell carcinoma.[v] In terms of down-regulation, wild-type p53 has been proposed to bind to the Survivin promoter in vivo and act to repress transcription of the Survivin gene.[6,7]

Survivin is the smallest mammalian protein member (16.5 kDA) belonging to the IAP gene family. As an essential regulator of cell proliferation, differentiation and death, recent studies have been attempting to elucidate the multifunctional Survivin-mediated signaling pathways that act at the interface between cell cycle progression and cell death inhibition.

Survivin is considered a chromosomal passenger protein that is involved in chromosome segregation, central spindle formation, cytokinesis, and spindle checkpoint maintenance through its interactions with inner centromere protein (INCENP), Aurora-B kinase (Aurora-B), and other passenger proteins.[8] At the onset of mitosis, Survivin associates with the microtubules of the mitotic spindle apparatus. Disruption of the Survivin-microtubule interaction results in the increase of caspase-3 activity and the loss of the anti-apoptotic function of Survivin.[9] Survivin's oncogenic potential therefore results from its ability to overcome the $G_2$/M checkpoint to ensure mitotic progression.[10] This interaction between Survivin and microtubules of the mitotic spindle apparatus appears to be necessary to prevent a default induction of apoptosis at the $G_2$/M phase of the cell cycle.

In general, IAP proteins negatively regulate apoptosis-inhibiting caspase activity. Caspases are cysteine proteases that form a proteolytic network that is responsible for cleavage of other proteins in the mechanism leading to apoptosis. IAPs target a downstream step in apoptosis by direct inhibition of the terminal effector caspases-3 and -7[10] and by interfering with processing and activation of the pinnacle caspase, caspase-9, thereby preventing initiation of the intrinsic caspase cascade.[11] Specifically, Survivin may bind to the p20 subunit of caspases-3 preventing the second catalytic cleavage necessary for its activation.[12]

However, Survivin's role in this apoptotic pathway has recently become contentious as Mak in Toronto have reported that while Survivin maintains vital functions in both cell death and proliferation in vivo (via mitosis progression), it does not seem to directly regulate apoptotic pathways.[13] However, their findings did also suggest that Survivin-deficient cells exhibited abnormal spindle formation, especially in rapidly forming spindles, therefore inducing severe defects in chromosome segregation and cytokinesis.

Furthermore, three alternatively splicing transcripts have been identified in a single copy of the Survivin gene. In addition to wild-type Survivin, two novel variants (survivin-2B and survivin-DEx3) have been generated. They may have distinctive roles in apoptosis especially considering that they may present in different sub-cellular locations. In recent studies, the frameshift carboxyl terminus of Survivin-DEx3 was found to contain a bipartite localization signal, which mediates its strong nuclear accumulation and may interfere with degradation of Survivin-DEx3 protein by ubiquitin tagging.[14] In contrast, Survivin wild-type and Survivin-2B are likely found in the cytoplasm.

The significance of the nuclear/cytoplasmic localization of Survivin is controversial and often depends on tumor type. Zangemeister-Wittke and Simon hypothesized that Survivin inhibits apoptosis by interacting with caspases-9 in the cytoplasm, but in the nucleus, Survivin binds to microtubules and assists in chromosomal segregation and cytokinesis during mitosis. Translated, the nuclear pool of Survivin may be involved in promoting cell proliferation, whereas the cytoplasmic pool may participate in controlling cell survival but not cell proliferation.[15]

Unlike the anti-apoptotic members of the Bcl-2 family or other IAPs, Survivin has been largely described as being undetectable in normal terminally differentiated adult tissues but becomes notably expressed in common cancers. Survivin has been regarded as a marker of malignancy in such tumors of the brain, lung, breast, colon, stomach, esophagus, pancreas, liver, uterus and ovaries, Hodgkin's disease, non-Hodgkin's lymphomas, leukemias, myelodysplastic syndromes with refractory anemia, neuroblastomas, pheochromocytomas, soft tissue sarcomas, melanomas, and namely, in head and neck squamous cell carcinoma (HNSCC).

## Primary HNSCC

To date there are very few molecular markers that have proven to be sufficiently strong indicators of treatment response or prognosis of HNSCC. In particular, there have been limited reports describing how Survivin expression is specifically related to tumors of varying anatomical subsets. Recently, Sharma *et al.* found that 43/50 HNSCC cases investigated showed significant positive Survivin immuno-staining when compared to controls. It was concurrently found that while Survivin expression was significantly associated with the degree of differentiation of the HNSCC tumor, no significant association with age, sex, smoking index or alcohol consumption was found. Overall, Survivin expression in HNSCC was strongly associated with reduced apoptosis thereby suggesting a pathobiological etiology for tumorigenesis. The following highlights how Survivin expression is associated with Oral, Nasopharyngeal, and Laryngeal cancers, and the particular cellular localization of the Survivin protein in each sub-site.

## Oral SCC

OSCC is the tenth most common form of cancer, comprising 2-3% of all new malignancies diagnosed in the United States.[16] Within the oral cavity, squamous cell carcinoma is the most frequent malignancy found and is typically associated with local spread. The incidence of metastasis traditionally depends on the degree of cellular differentiation, depth of invasion and specific site of primary tumor in the oral cavity. Examining 78 cases of OSCC, Lo Muzio *et al.* have found that Survivin expression may identify patients at risk of more aggressive and disseminated disease. Survivin was also significantly associated with patient survival in Lo Muzio's study that followed patients for 72 months.[17] These findings are further confirmed by Kim et al. who had found that Survivin expression had significance as an independent prognostic risk factor for OSCC patients.[18] They found that the Survivin positive cohort had 2.5 times greater OSCC risk than the negative group. From these studies, it is postulated that Survivin could be employed as a potential marker of aggressive tumors, and potentially guide management by indicating for closer follow-up protocols and/or alternative combined treatment regimens.

In terms of cellular localization, Marioni *et al.* found that in Survivin-positive oral and oropharyngeal primary SCCs and lymph node metastatic cells showed prominent nuclear staining. This suggests that in OSCC, Survivin may act to promote cellular proliferation.

## Nasopharyngeal SCC

Nasopharyngeal carcinoma (NPC) represents the third commonest tumor seen in the head and neck. Clinicopathological parameters such as clinical stage, histological type, tumor grade and the patient's age, may reflect the aggressiveness of NPC and the often dismal clinical outcome. Zhang et al. were one of the first groups to demonstrate that Survivin was over-expressed in NPCs. This group found that Survivin was expressed in 47.92% (n=48) NPC patients and that its expression was negatively associated with cell apoptosis (apoptotic index). Survivin also appeared to have a role in NPC tumorigenesis and its over-expression was found to be significantly associated with progression of NPC stage (T3 + T4 vs. T1 + T2) and poor clinical prognosis.[19] Multidisciplinary Toronto research groups have recently provided corroborative data demonstrating the role of Survivin in NPC and as a potential target for molecular targeting for treatment.[20] In fact, a recent publication from Toronto proposed a unique bimodal response to Survivin expression in NPC. Both low and relatively high levels of expression were found to be significant for biological aggressiveness and subsequent poor clinical outcomes.[21]

The dismal prognosis of NPC has also been related to its late diagnosis and its associated advanced stage. In Toronto, Freeman and Irish proposed nasopharyngeal brush biopsies to evaluate early stage NPC.[22] Correspondingly, Smith *et al.*

reported that Survivin was detected in the urine samples of patients with new or recurrent bladder cancer.[xxiii] Therefore it seems that Survivin expression in bodily secretions can be screened for markers of malignancy. These recent findings suggest an alternative paradigm for diagnosis of early stage NPC by evaluating Survivin expression in nasal secretions.

### Laryngeal SCC

Laryngeal squamous cell carcinoma is the eleventh commonest form of cancer in men worldwide.[xxiv] The prognosis of LSCC is related to the site, size and the stage of tumor. Pizem *et al.* demonstrated Survivin expression of varying proportions in 67/68 LSCC cases.[25] Specifically, this group found that Survivin expression in endothelial cells was consistent with angiogenesis in LSCC and that over-expression of Survivin predicted a poor clinical survival. In Dong's study, 65.7% of LSCC tumors were Survivin positive and this group additionally reported that Survivin expression was significantly associated with tumor size, poor differentiation, tumor size, lymph node metastasis and advanced stage.

In terms of cellular localization, Pizem *et al* found a Survivin nuclear reaction predominated in their laryngeal carcinoma biopsies. Similar to OSCC, Survivin appears to work via a cellular proliferation model in the laryngeal subset of tumors.

### Lymph Node Metastasis

To achieve improved locoregional control, the lymphatic networks of the head and neck must be assessed. However it has been a challenge to identify the true extent of treatment based on clinical examinations and varying imaging modalities. For example, in HNSCC patients with clinically negative necks (N0), the incidence of micrometastasis in postoperative histopathologic sections is approximately 30%.[26] Since early HNSCC diagnosis and treatment can be important for an increased survival rate, evaluating primary tumors for Survivin expression may provide clues to help navigate patient management strategies of N0 necks.

Reports still provide contrary data regarding Survivin expression in primary HNSCC and the presence of lymph node metastasis. Dong *et al.* studied 102 cases of laryngeal SCC and reported a significant association between positive Survivin expression and lymph node metastasis.[27] While Lo Muzio's review of 110 cases of OSCC reported no significant correlation between expression and lymph node metastasis,[28] he later found a significant increase in Survivin expression associated with 46 OSCC metastatic cases.[29] Marioni et al. found that Survivin expression was significantly higher in primary oral and oropharyngeal SCCs with lymph node metastasis that in those without (n=26).[30] However, Sharma *et al.* reviewed 50 cases of HNSCC (38 laryngeal and 12 oropharyngeal) and found no significant association between expression and nodal metastasis.[31] These findings suggest that Survivin expression in primary oral and oropharyngeal SCCs may identify patients at risk of disseminated disease. Surgically, this can translate to elective neck dissections in clinically N0 patients with primary SCCs that demonstrate a high level of Survivin expression.

While the gold standard for detecting lymph node micrometastasis has been Hematoxylin and Eosin (H & E) staining, it is becoming too impractical, expensive and time consuming for routine practice. Therefore, target gene transcript amplification in lymph node specimens has been suggested. Lo Muzio *et al.* studied Survivin expression in six lymph node metastases from OSCC and stated that all of them were positive. In contrast, Marioni *et al.* found that only 61.5% of cervical lymph node metastasis to be Survivin positive. These findings suggest that clearly more research is needed to elucidate the role for target gene transcript amplification of Survivin in the identification of metastasis from primary HNSCC.

### Diagnosis using Auto-Antibodies

Auto-antibodies can be induced by several cellular molecules when cells are in a high-proliferation state, such as in malignancy. In particular, oncogenic protein markers have been found to induce an auto-antibody reaction. For example, auto-antibodies to p53 are detectable in serum and thus may serve to monitor tumor progression and/or response to treatment. Antibodies have also been associated with high grade tumors or poor clinical prognosis.

Recently, Chang *et al.* developed an enzyme-labeled assay to measure anti-survivin auto-antibodies in sera from 294 patients (81% OSCC) before cancer treatment in Taiwan.[32] It was found that anti-survivin antibodies were increased in 46% of these cancer samples. This study showed that anti-Survivin antibodies were correlated with tumor aggressiveness, thereby indicating that serum auto-antibodies may represent cellular status. This innovative research suggests that simple rapid enzyme linked assays, using recombinant Survivin protein as the antigen, may be advantageous for non-invasive screening of healthy individuals or those at risk of HNSCC. This information can then be used to guide diagnosis, prognosticate or to monitor tumor response to treatment.

### Treatment Possibilities

From advancing research in the basic sciences, it appears that understanding the biology of HNSCC at the molecular level appears to be a prerequisite to improving the therapy of the disease. It has been suggested that cancer cells return to a fetal pattern of Survivin expression to enhance cell viability, resist apoptotic stimuli and thereby become capable to overcome the cytotoxic effects of chemotherapeutic agents.[33] Furthermore, it has been seen that Survivin-transfected cells demonstrate resistance to anticancer drug-induced apoptosis.[34]

Survivin directly blocks the processing and activation of caspases-3 and -7 which act downstream to the two major apoptotic pathways; the mitochondrial pathway and the death receptor pathway. Cisplatin and Etoposide are commonly used for the treatment of advanced as well as recurrent and metastatic head and neck cancers and correspondingly, it has been established that these genotoxic drugs work via the same members of the caspase family that are involved in Survivin mediated apoptosis. Also of interest is that Cisplatin acts in the $G_2$/M phase of the cell cycle; the same

period as Survivin's activity.

Antisense oligonucleotides have become increasingly efficacious due to the advances in oligonucleotide chemistry, such as the introduction of a phosphorothioate backbone which makes it more resistant to degradation by nucleases.[35] Antisense oligonucleotides that reduce the expression of Bcl-2 have been shown to inhibit the growth of tumor cells and sensitize tumor cells to chemotherapy. For example, early evidence suggests Oblimersen sodium, an antisense oligonucleotide that binds to Bcl-2 mRNA, produces positive results in a variety of cancers when it is used in combination with chemotherapy. Correspondingly, antisense-mediated reduction of Bcl-XL induces apoptosis in a gastric cancer cell line.

Therefore the Survivin antisense approach has intriguing potential. To date, the Survivin antisense approach has been found to inhibit tumor proliferation and induce apoptosis in preclinical models such as liver cancer cells,[36] ovarian cancer cells,[37] melanoma cells,[38] colon[39] and lung cancer cells.[40] However, there are very limited studies investigating if the Survivin antisense approach has a valid therapeutic effect in HNSCC.

Recent evidence suggests antisense oligonucleotides that reduce Survivin expression, also induce apoptosis, polyploidy and sensitize tumor cells to chemotherapy in vitro.[41,42]

Kojima *et al.* has found that a replication-deficient adenovirus encoding a Survivin antisense gene down regulates Survivin expression and activity, causes spontaneous apoptosis in KB cells, and inhibits tumor growth in a mouse model of HNSCC.[43] When combined with Cisplatin, this group discovered antisense-mediated down regulation of Survivin can sensitize tumor cells (KB cells) to chemotherapy in vitro and in vivo.

Using a 206bp Survivin antisense oligonucleotide in combination with Cisplatin and Etoposide (which triggers cell death via cytochrome c release), Sharma, Lo Muzio and Mariggio also provide indirect evidence that down-regulation of Survivin expression sensitizes cells to death induction via the mitochondrial pathway.[44] By reducing caspase-3 and -7 generation, anti-Survivin has been shown to facilitate cell death with the hallmarks of mitochondrial-dependent apoptosis; release of cytochrome c and loss of mitochondrial transmembrane potential.

Expression of Survivin in endothelial cells results in a cytoprotective response counteracting apoptosis, reducing the generation of active caspases, and preserves cellular survival. More importantly, Survivin appears to stabilize the three-dimensional capillary networks in vitro providing a proangiogenic response. Altieri's recent work has proposed that Survivin expression during angiogenesis may provide a pivotal advantage factor to maintain a florid blood supply during tumor growth. Furthermore, antisense Survivin targeting during angiogenesis caused endothelial cell apoptosis and promoted involution of capillary-like vessels in vitro. Kerbel *et al.* and his Toronto group have also suggested that targeting Survivin might inhibit tumour growth by inducing involution of tumor blood vessels.[45,46] Therefore it seems that greater tumor control can be accomplished with treatment of anti-angiogenically potent chemotherapy, particularly microtubule-inhibiting drugs.

Overall, these studies illustrate that Survivin functions as a novel upstream regulator of mitochondrial-dependent apoptosis, and molecular targeting of this pathway results in anticancer activity via a dual mechanism of induction of tumor cell apoptosis and suppression of angiogenesis.

## Conclusions

Molecular markers are receiving increased attention in HNSCC as oncologists attempt to improve morbidity and mortality. Understanding the mechanism of tumorigenesis is vital in determining new ways to achieve early diagnosis and prognosticate head and neck squamous cell carcinoma. It is clear that Survivin is involved to some degree in HNSCC and we are only now discovering its complex relationship to tumorigenesis. Survivin may also help us determine the etiology of the cancer and help identify new risk factors. For example, HPV-16 has been found to up-regulate endogenous Survivin.[47]

Some data suggest that Survivin may be able to predict advanced cancers and therefore help the oncologist appropriately manage complex cases. Early diagnosis of NPC by screening nasal secretions for Survivin appears interesting, as does assessing the degree of Survivin expression to help guide elective neck dissections for clinically negative necks. Also insightful is the role of auto-antibodies for diagnosis of HNSCC but its role in this subset of cancers may be limited by the number of other malignancies that express Survivin.

In terms of improving treatment, it seems that while Survivin antisense therapy may not be potent for stand-alone chemotherapy, it may have some potential as and adjuvant in managing HNSCC. It is becoming increasingly clear that multimodal treatments using anticancer agents with different sites of action and non-overlapping toxicities are more successful that single agent therapy. Thus, employing antisense-Survivin therapy can potentially allow for the use of lower doses of chemotherapy for treatment of HNSCC, therefore potentially decreasing side effect severity.

Toronto appears to be working on multiple fronts to elucidate the role of Survivin in cell biology and cancer. We need to now be able to apply molecular advances to clinical applications in head and neck oncology. Hopefully, understanding the molecular nature of HNSCC will eventually help us optimize the management of our patients. Thus it is imperative to further elucidate Survivin in head and neck squamous cell carcinoma and advance our understanding of the role for anti-sense Survivin treatment.

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# Highlight: Campaign for Healthier Care

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With a variety of challenges surrounding today's Ontario Health Care system, much of the provincial government's attention has been focused on fixing the acute health problems and providing temporary solutions in meeting Ontario's current health care needs. The growing pressure from the public to see immediate tangible results in health care has led to the province seeking and even scrambling for quick-fixes, rather than anticipating problems. In the face of the Severe Acute Respiratory Syndrome (SARS) crisis, the epidemic exposed the weakness of Ontario's public health infrastructure and its inability to respond to the reality of biological globalization. As Justice Archie Campbell concluded in the SARS commission on January 2007, "there was no system in place to prevent SARS or to stop it in its tracks."[1]

Ontario's demographics are extremely dynamic. The robust growth of Ontario's population is projected to increase by as much as thirty percent, or another 3.8 million, in the next twenty-four years. More importantly, the growth in the seniors' share of the population will accelerate after 2011 and the proportion of the population over the age of 65 will double by 2031.[2] With the population increasing in age, the incidence of common age-related conditions such as cancer, Alzheimer's disease, cardiovascular disease, and diabetes mellitus are estimated to increase by at least 75%.[3,4,5,6,7] The growing number and complexity of the needs of seniors alone will place a great demand on an already overburdened health care system. The current system will not have the capacity to appropriately serve the future needs of Ontario's patients.

The reality of these health and population projections has prompted the Ontario Medical Association (OMA) to develop the "Campaign for Healthier Care". The campaign is a three year multi-phase strategic communication program that aims to increase public awareness of the state of the current health care system and begin to challenge Ontarians to start thinking about the decisions and actions they must take to ensure a sustainable system in the future. The OMA has already aggressively advertised the campaign through major newspaper and media coverage, as well as by providing information packages to offices, conferences, and communities. Each phase of the campaign is to be individually unveiled over the course of three years as the public and health care stakeholders' inputs are thoroughly discussed and debated. As the former OMA President has indicated, the campaign hopes to "to shift the health care dialogue away from crisis management and towards a long-term vision of health care in Ontario, the strategy to respond to that vision."[8]

### Phase I – Ontario's Doctors Asking Questions

Educating the public about the multi-dimensional challenges in administering patient care and treatment is an integral component of the campaign. Six scenarios are presented in the campaign's discussion paper, which explores the various facets of providing patient care and engages the reader to question the feasibility of today's health care system. This gives rise to five questions that form the basis of the campaign's first phase.

The five fundamental questions are:[9]

1. Given that Ontario will be hit with a massive need for acute and chronic care in the next 20 years, how will we make sure that the health care system is ready?
2. The need for home and community care is growing rapidly, but how will we make sure that people get the care they need, where they need it?
3. How will we do more, and earlier, to detect and prevent disease?
4. How should we think about the economics of health care going forward?
5. How should we think about the role, rights, and responsibilities of the patient?

These questions are considered by the OMA as provocative, yet critical, in helping shape and prepare the public's thinking about the future of Ontario's health care. It is a starting point for Ontarians to begin their conversation in finding a long term solution that would meet the need for acute and chronic care in the next few decades.

### Phase II – Ontario's Doctors Thinking Ahead

The OMA has recognized the tremendous magnitude of the change they are about to undertake. Thus, to adequately address their five fundamental questions, they have developed six principles which will help guide them forward.

The six principles of healthier care are:[10]

1. Keep the patients front and center.
2. Focus on the future.
3. Be specific – focus on changes that will have maximal impact in access to quality care.
4. Think investment, not cost.
5. Apply what we know faster – ideas that have been proven to work should be implemented now.
6. Start now.

These guiding principles lay the groundwork for the next phase of the campaign and provide a specific focus for Ontarians to aim and strive for. The goal of the campaign's actions should now be in parallel with these six principles. The principles maintain the urgency of the OMA to focus and act for the greater good of the future of Ontario's patients.

### Phase III – Ontario's Doctors Moving Ahead

With the provincial election underway, the OMA is prepared to press forward and to act on their previous phases. They prepared four crucial steps, which the province must now take to ensure the sustainability of the future health care system.

The four priorities are:[11]

1. Fix the shortage of Health Care Professionals.
2. Implement the patient e-record.
3. Ensure the right care when, where, and how people need it.
4. Commit to raising a generation of healthier kids.

These four priorities are not only in line with anticipating future problems, but also addresses four major problems in today's system: human resources, e-health, home and community care, and prevention. These priorities are also sent directly to the government and to individually nominated candidates in the upcoming provincial election to inform them of the change following the election. Supplementing this position paper is a full policy questionnaire which the OMA has sent in the hopes of receiving full government support on their initiatives in the future. A total of five yes/no questions have been asked of each candidate: [12]

1. Given that there is an intense national and international competition for Ontario's doctors, do you support the development of a comprehensive retention strategy to encourage practicing doctors to stay in the province?
2. Given that patients in Ontario deserve timely access to quality care, do you support the need to measure the wait time for all procedures and of the full wait time – from the time a patient is referred by a family doctor?
3. Given that electronic health records greatly enhance patient safety and improve efficiency in the system, do you support a significant investment into e-health capabilities in the province?
4. Given that Newfoundland, Quebec, Saskatchewan, and most recently Alberta have all adopted a policy to defer provincial government student loans until completion of residency training, and that Ontario needs to stay on par with other provinces to remain competitive in physician recruitment and retention, do you support interest deferral for Ontario's medical students?
5. Do you agree with dedicated provincial support to ensure that every Ontarian has access to a family doctor?

### The Next Phase

The next few phases of the campaign will be unveiled and issued over the course of the next few months. Despite the fact that the road to Healthier Care is still under continuous discussion and development, it is clear that Ontario must place the future of the patient's needs at the forefront of their agenda. The OMA has provided the leadership on an innovative initiative in campaigning for the future of Ontario's health care system, however, it will take a collective commitment from the government, health care stakeholders, and all Ontarians to create a powerful force that will bring about a sustainable change in our current system. The future is now and we must embrace the change.

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