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LA REVUE CANADIENNE DE MÉDECINE INTERNE GÉNÉRALE

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Knowledge as Practice: Rethinking Medical Education
Kuper

Disseminated Herpes Zoster in an Apparently Healthy Middle-Aged Woman
Wilson et al.

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ABOUT THE COVER

The cover photo, a trompe l'oeuil mural in Quebec City, was taken by Peter Ashton during a tour of Canada. Born in Prestbury, Cheshire, England, Peter has lived in Aylesbury, Buckinghamshire, since 1973. He was a biomedical scientist and took early retirement from his post as blood bank manager at Stoke Mandeville Hospital in 2002. Peter's interests include photography, travel, and collecting banknotes. He is an active member of the University of the Third Age (U3A). More of Peter's photos can be viewed on www.flickr.com/photos/peamasher/sets.

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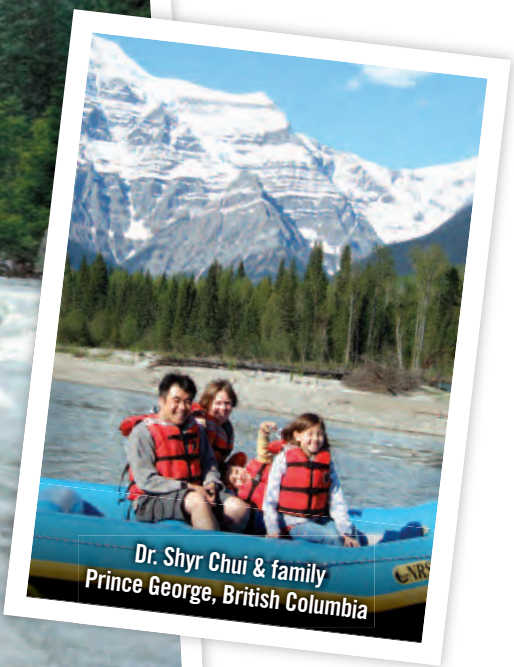

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"Keepers of the Meaning"

Donald Farquhar MD SM

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Albert Schweitzer once remarked, "Example is not the main thing in influencing others. It is the only thing."

How true that is in so many spheres, but particularly so in the health professions. Former Queen's University vice-dean of medicine Dr. Robert Maudsley observed that, of the four fundamental components of medical education – planned and organized curriculum, structured experience, role modelling and the learning environment – role modelling is considered the most important, by far, by medical school deans.[1]

Role models serve as what Harvard psychiatrist Dr. George Vaillant, in his landmark longitudinal study of adult aging and development, referred to as "keepers of the meaning."[2] In their deeds and demeanour, our role models capture the essence of what it means to be a good doctor, teacher or scientist, and inspire us to reach for the same level of excellence.

Mentors are senior teachers or advisors who invest time and energy in the professional development and personal growth of younger colleagues. Not all role models become mentors, but with rare exception, all mentors are role models. Mentors provide guidance, counsel, coaching, constructive criticism, sponsorship, intellectual stimulation, and moral support, in a relationship that often spans many years, and that is as fulfilling and meaningful to them as it is to their protégés. Fortunate indeed are those who have been privileged to receive – and give – mentorship.

Canadian physicians who practise, teach, and advance the art and science of general internal medicine can look to many role models and mentors who have influenced our thinking and shaped our discipline – from William Osler to Robert C. Dickson, Alan Gilbert, Herbert Ho Ping Kong, Rene Roux and Bill Spaulding, to name just a few. Some, such as these, achieve recognition beyond the borders of their own practices. Others, while less renowned, are equally seminal in the professional development of those who fall within their sphere of influence.

With this issue of the *Journal*, we are launching a new section titled *The Oslerian Tradition*, in which we celebrate and reflect on our own "keepers of the meaning" – personal accounts of those role models and mentors who have personified the best of our traditions. And in a companion section, *Oslerian Diaspora*, we highlight the ongoing innovations and achievements of our colleagues in general internal medicine across Canada. Through these new sections, we hope that the *Journal* can assist in building and fostering a strong sense of continuity and kinship within our vibrant and growing specialty.

Readers of this fall's edition will notice a slightly new look to the *Journal*, with what we trust are more attractive colour banners and headline fonts, and a consolidation of our various sections into *Clinical Medicine; Diagnostic Approaches; Clinical Pharmacology and Therapeutics; Original Observations and Research; Teaching and Learning; Health Promotion, Policy, and Advocacy; Patient Care Quality and Safety; Physician Health; Case Reports;* and *Humanities and Bioethics*. In this issue's *Teaching and Learning* section, we feature reports from colleagues at McMaster University of innovative programs in global health and medical simulation, and a thought-provoking essay by last year's CSIM New Investigator Award winner Dr. Ayelet Kuper on "rethinking medical education." In future issues, we will return to more practice-oriented articles and will also begin to include a sampling of original observations and research.

We are deeply indebted to our former editor-in-chief and now editor emeritus, Dr. Hector Baillie – a true keeper of the meaning and of the faith – for his patient and determined stewardship of the *Journal* through its first six volumes. As we continue to develop the vision and content of the *Journal*, we look, as always, to the membership of the Canadian Society of Internal Medicine for its input and guidance, to ensure that we are meeting the needs of the general internal medicine community in Canada.

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Knowledge as Practice: Rethinking Medical Education

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There is a long tradition of general internists being involved in medical education as teachers, educational administrators, and, increasingly, medical education scholars and researchers. In recent years, the medical education journals have contained rather lively and impassioned debates about the best ways in which to carry out that sort of research. During the first years of the 21st century, editorial debates in the top journals in the field (e.g., *Medical Education, Academic Medicine, Advances in Health Sciences Education*) were divided on such basic issues as these: (1) What are the most important research questions that medical education research should be addressing?[1–3] (2) Who is the target audience of that research – the deans and course directors and clinical teachers, or other researchers in the field?[3,4] (3) Which research methodologies should be used?[5–10] These issues were also discussed at conferences, in meetings, and informally among colleagues.

What was going on? And does it matter? Through my research, I've come to understand that such debates really do matter because the ways in which we think about and do research allow us to study certain things while hiding others.

In order to understand these debates within medical education research, we need to clearly define a key term that is used in everyday language but has a particular meaning in this research context: *legitimacy*. The work of sociologist Pierre Bourdieu showed that every research field, like every other field of practice, can be described as a field of struggle for legitimacy and power.[11–15] Everybody who claims membership in a particular field wants to succeed in that field – to win at that "game."

Take, for example, the field of art, which, like all fields, constitutes a field of struggle and competition for what is "good." The history of 20th century European art reveals that what was thought of as good art in 1880 is very different from what was thought of as good art in 1920 or in 2000. Producing realist bronzes today, such as Rodin did in the 1880s, would probably not get an artist much money – which in the art world is part of the currency for legitimacy – or a big solo show in a reputable gallery – which is another part of what gives an artist a certain kind of legitimacy. It also wouldn't get an artist loud acclaim from art critics, a professorial job in a fine arts department, or laudatory books by serious art historians – which are other things that give an artist a different kind of legitimacy. So, in his day, Rodin might have been "it," but since then other artists have changed the rules of the game. Some try to be shocking in order to be trendy, to be "the next big thing," while others make an effort to do work that expands our understanding of art or connects art to society in a new way. It just depends on which legitimacy game they're playing.

In science, as in art, some people do well by playing by the current rules of the game – by doing the kind of research that is already recognized as good, as legitimate. Everybody wants to be able to publish their research in the "best" journals and speak at the "best" conferences, whatever *best* means in their particular field. Some people accomplish that by doing the kind of research that is already accepted in their field; by doing something already seen as legitimate, they legitimate themselves and their research.

However, if people who do novel or unusual kinds of research also want to succeed, they have to redefine what counts as successful. That might, for example, mean helping the smaller journal in which they publish, or the more obscure conference where they present, become more successful and so more legitimate – and more legitimating to those who present or publish there. It might also mean reshaping the definitions of research productivity in their departments (e.g., their promotion criteria) to allow research about new subjects, and to include publications in what were initially much less prestigious journals. It means changing the rules of the game – changing the definition of legitimate research to make it match what they do.

Needless to say, the people who are already doing well by the

current rules of any game, be it science, art, or Monopoly, don't want those rules changed. Struggles therefore ensue. In medical education research, as in other scientific fields, these struggles usually take place in the public forums of the field – in its journals and conferences. With this understanding, we can see that medical education research has been having all these debates in the literature because of an ongoing struggle for the definition of legitimacy in that field.[16] In that case, what have they actually been struggling about? Just as artistic legitimacy is about good art, scientific legitimacy is about "good knowledge." More specifically, it is about producing "legitimate knowledge" in legitimate ways. Are the debates in medical education research actually about legitimate knowledge and its production? Let's revisit some of the issues they've been debating.

What Are the Most Important Research Questions That Medical Education Research Should Be Addressing?

The issue of the most important research questions that medical education research should be addressing is certainly about what knowledge should be counted as important, funded, and published. From a sociological perspective, people can be expected to advocate for the kinds of knowledge they produce or otherwise benefit from, whether individually or through the prestige of being attached to a group that produces that kind of knowledge. Not surprisingly, there is no actual consensus on these "most important research questions," even within the Canadian context. As a case in point, the undergraduate medical education component of the Association of Faculties of Medicine of Canada's Future of Medical Education in Canada project[17] identifies at least 10 major priorities and many smaller niche issues, while the draft report of the residency component[18] includes seven different priorities, each with between three and 11 action items; almost all of these would require research to support their implementation or evaluation.

Who Is the Target Audience of That Research?

The question of the target audience of medical education research has recently been the subject of sociological research, which found that there is an important debate between two camps of medical education researchers: those who see legitimate knowledge production in their field as being for other producers of that knowledge (i.e., for other medical education researchers), and those who see legitimate knowledge production as being for users of that knowledge (i.e., to serve the practical needs of the teachers and administrators with and for whom they work).[16,19] The production-for-users camp was winning for a while, but there has recently been a resurgence from the production-for-producers camp, the "basic scientists of education," arguing for theoretically based research programs[20–24] rather than for research that answers immediate curricular and pedagogical needs.

Which Research Methodologies Should Be Used?

The question of which research methodologies should be used in medical education research, which is directly about legitimate ways to make new knowledge, is a major issue in medical education research right now. As an interdisciplinary field, medical education research increasingly draws in researchers from disciplines in the social sciences and the humanities who ask the kinds of research questions that require whole different sets of research tools from the randomized controlled trials common in clinical medical research. Many medical education researchers do conduct statistical research, but the highest impact factor journals within medical education research are now strongly advocating a diversity of methodological approaches. Whereas even 5 years ago qualitative research was relegated to the fringes of big international medical education meetings such as the annual conference of the Association for Medical Education in Europe (AMEE), over the past several years it has clearly become an accepted component of those meetings.[25] The medical education journals, which used to be tightly modelled after medical journals, have recently increased their word limits to accommodate qualitative research papers. Methodologies such as grounded theory, ethnography, and discourse analysis, each with its own decades and sometimes centuries of tradition and rules and markers of rigour, have become increasingly popular in medical education.[25,26] All of this is happening despite the fact that the people with the most money and power in the field – the research users, generally physicians, who still authorize and fund a fair amount of medical education research (and in whose clinical departments most medical education researchers work) – don't always understand these methodologies, don't think they're legitimate, or sometimes don't even know that they exist! Understandably, confusion ensues as the struggle for the definition of legitimate knowledge production continues.

Discussion

This last issue, of legitimate research methodologies, is a major subject area of my own research. I want to understand why medical education research decided, at one point in time, that certain ways of producing knowledge were legitimate and other ones weren't, and then why, at other points in time, the situation changed. For example, why did psychometric research (the statistical science of educational measurement, of test reliability and validity) dominate medical education research for several decades,[27] and why is psychometrics no longer so dominant?[25,28] My first study in this area identified and analyzed the early days of the field, which my research dated to the mid- to late 1950s. My

work identified socio-historical factors that enabled and promoted the emergence of the field in that place, at that time, and in that particular way.[29] I also found that, in the early days of the field, some specific disciplines (e.g., psychology, sociology, education) developed an increased research focus on medical education, and the different ways in which this focus was operationalized are linked in the historical material to their various perceptions of legitimate research.[30,31] Some disciplines also worked harder than others to increase the legitimacy of their methods of knowledge production in the eyes of the medical education establishment (the knowledge users).[30,31] For example, at one large meeting of senior medical administrators, mostly deans, organized by the Association of American Medical Colleges in 1956, a group of psychologists worked hard to show the importance of their type of research. Their rhetoric was impressive; one even gave a speech that proclaimed to the doctors that "psychology puts in your hands the power to change the nature of the entire profession. Such power is almost frightening, but refusal to use it may be an abdication of responsibility."[32] Texts from that era show that the psychologists made a huge impression at this meeting[33]; with the support of the doctors whom they were addressing, they went on to dominate the medical education research agenda for many years to follow. In other words, all of their hard work at legitimizing their knowledge was successful – for a time.

These issues of legitimacy and knowledge from decades ago are echoed in those we encounter today. By following this history forward in time, one can trace the social dynamics that continue to shape this field and so illuminate its present-day debates. This may seem rather abstract, especially for those used to more practical education research. It is, however, analogous to basic science research in any other field – it sets the underpinnings and leads to new possibilities in other, perhaps more practical domains. For example, by challenging the roots of our conceptions of legitimate research, it allows us to present, as a potential way forward out of some of these debates, the idea that a broader definition of "good research" might be attainable if we could try to understand (at the very least) how *good* is defined differently in the domains from which we've borrowed the different methods we're now using.

What is, however, even more important about an understanding of how we came to have certain legitimate ways of producing knowledge in medical education research is that the narrow kind of research that medical education used to think was legitimate both limited and guided the kinds of questions education researchers were able to ask and to answer. There were things we couldn't study – or couldn't study well – and, as it has been argued in the literature, our educational practice was therefore also limited to the things that our research methods were well oriented to study.[34,35] That's what happens when, as is almost inevitable, we privilege certain methods of knowledge production in any field. It can hide important research questions and, more importantly, conceal useful ways of finding answers.

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Designing and Implementing a Comprehensive Simulation Curriculum in Internal Medicine Residency

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Khalid Azzam (right) is an associate professor in the Division of General Internal Medicine at McMaster University, in Hamilton, Ontario, and also serves as assistant dean for continuing health sciences education, director of simulation for the Internal Medicine Residency Program, and internal medicine clerkship coordinator at the Hamilton Health Sciences Centre (HHSC), Hamilton General Site. He is also a consultant with the Bariatric Medicine Clinic, HHSC. Parveen Wasi is a professor in the Department of Medicine, at McMaster University. Ameen Patel is a professor, department education coordinator, and attending physician in the Department of Medicine at McMaster University. Correspondence may be directed to azzamk@HHSC.CA.

Medical simulation is the use of a device or series of devices to emulate anatomy, real-life clinical situations, and clinical procedures for the purposes of education, evaluation, and research.[1,2] Simulation is a powerful tool in the education and evaluation of physicians and is rapidly becoming a central thread in the fabric of medical education.[3] The effectiveness of simulation-based medical education (SBME) can be optimized by integrating simulation into an overall curriculum.[4] Internal medicine training programs are introducing procedural training using simulation but are not as advanced as other programs, such as anesthesia and emergency medicine, in the use of technology-based simulation utilizing high-fidelity full-size mannequins.[5] We feel simulation can be used to teach a wide range of CanMEDS competencies, and a comprehensive simulation curriculum should become a standard in internal medicine residency training.

Benefits of Simulation-Based Training

Medical simulation complements traditional educational activities based on real patient-care experiences.[4] Simulation-based training (SBT) is becoming more and more important as the health care delivery is evolving with increasing outpatient management of complex problems, higher acuity of admitted patients, and shorter hospital stays. These factors, along with decreased resident work hours, all contribute to fewer exposures to real-life situations.[2,6] SBT is an effective tool that can be used to counter these obstacles and can be incorporated into a traditional curriculum or competency-based training. Simulators are readily available, help control for the variability of clinical exposures, avoid the ethical issues of training on real patients, and provide a standardized environment for immediate directed feedback.[2,7] The use of simulation improves mastery of knowledge,[2,6] learner satisfaction and confidence,[7,8] procedural skills,[5,7,9] and teamwork and communication.[4] Furthermore, upon retesting, knowledge, procedural comfort, and performance are improved.[7] In an emergency medicine program, trainees rated a novel simulation-based curriculum as highly effective and realistic. Residents responded favourably to replacing traditional lecture teaching with more active teaching formats, and, overall, they felt more satisfied with their learning experience.[10] The evidence also shows that patients are more willing to allow students to perform procedures on them after they have completed simulation training.[11]

Simulation Resources

SBT requires an initial capital investment for the purchase of equipment and ongoing funding support to replace parts and upgrade equipment. Success of an SBT also needs salary support for technicians and instructors. University- or hospital-based centres where resources as well as expertise can be shared make SBT more economical. Most of the internal medicine residency programs in Canada currently have access to university simulation centres. Postgraduate training programs should collaborate to ensure these centres maintain state-of-the-art technology and human resources and are available for all trainees.

A variety of levels of technical fidelity can be used to achieve the goals of an internal medicine program. These may include but are not limited to partial task trainers, full-body task trainers, and moderate- and high-fidelity mannequins. Partial task trainers provide the opportunity to learn and practise procedures that are considered "core training"

requirements by the Royal College of Physicians and Surgeons of Canada (RCPSC). These include lumbar puncture, central line insertion, joint aspiration and injection, thoracenthesis, and other procedures. Standardized patients (SPs), now a norm in medical training and evaluation, can be incorporated into hybrid simulation design where the SPs provide additional layers allowing for the creation of an increasingly complex curriculum that is designed with the flexibility to target residents at different levels of training. Full-body task trainers (e.g., Resusci Anne and MegaCode Kelly) and high-fidelity mannequins (e.g., SimMan) may be used to simulate complex medical scenarios.

Simulation Faculty

Recruiting faculty for simulation is challenging because of the usual reasons of time constraints, interest, and funding. Clinical teachers do not have the necessary skills to design and deliver simulation scenarios. This is becoming more evident with the use of more complex technology-based design and delivery such as that in full-scale simulation. Training continues to be a challenge. This is mainly due to the financial and time constraints that faculty experience when pursuing instructor training and the limited availability of instructor training offerings. Faculty development must be an integral part of every simulation-based curriculum. A simulation subcommittee that reports to the residency education committee can help to identify interested faculty, lead faculty development and explore research opportunities.

Curriculum: Design, Integration, and Evaluation

The curriculum design should include content, teaching strategies, and a formal evaluation process.[12] Programs should review the current residency curriculum blueprint to determine where simulation best fits within the curriculum. Collaboration among all stakeholders and local experts is important in identifying gaps in the current curriculum and assessing opportunities to use SBME strategies to fill these gaps. This consultation process can also identify areas in the curriculum with ineffective instruction modalities where the introduction of simulation, or the use of more advanced simulation, may better serve trainee learning needs and program goals. Once opportunities are identified, learning objectives should be determined and used to design teaching and evaluation modules that would include appropriate didactic content and simulation scenarios using a standardized format. The curriculum is best designed within the framework of the RCPSC CanMEDS competencies. This framework defines the key competencies needed for medical education and practice and is based on seven core roles: medical expert, communicator, collaborator, manager, health advocate, scholar, and professional. Modules of varying complexity can be developed and integrated in a graded manner across the 3-year training program. Many modules, or components of these modules, could be generalized for use in other programs.

Inter-professional training should be a key part of the simulation curriculum. Through the needs assessment process, programs should explore local trends in the complex interdisciplinary and inter-professional practice environment. Full-scale simulation scenarios can be scripted to reproduce complex situations, including ethical dilemmas, communication challenges, risk management issues, team dynamics, and cultural challenges that will target behavioural and cognitive skills training. Issues that could be taught through simulation include, but are not limited to, hierarchical barriers to communication; the inter-professional team environment of physicians, nurses, and other health care providers; and interface issues between the most responsible physician (MRP) team, rapid response team, and code team.

Evaluation is an essential step in curriculum design. Each simulation module developed must be validated and then evaluated using the Kirkpatrick evaluation model. This model measures the learner's reaction, the resulting increase in knowledge and capability, and the change in behaviour and performance. Anonymous surveys could assess the effect of the simulation curriculum on the learners. Feedback from learners should be incorporated in the development and improvement of the curriculum. The use of objective structured clinical examinations (OSCEs) and direct observation could assess certain technical and non-technical skills. Impact on knowledge and behavioural and cognitive skills could be assessed through changes in third-party evaluation (e.g., the Medical Council of Canada Qualifying Examination and RCPSC examinations) and supervisor evaluation. The impact of SBT on learners' overall performance and patient care is the most important; however, perusing such a measure is resource and time intensive.

Discussion

Technology-based simulation, using partial and full-body mannequins, was introduced into the Internal Medicine Residency Program at McMaster University in January 2009. We used partial task trainers for all levels of training. This initial experience was evaluated by surveying residents. Participants found the models to be useful training tools and agreed that these sessions improved their skills and confidence and provided information needed to perform the procedures safely. In June 2009, we conducted an inter-professional full-scale simulation, using a high-fidelity simulator (SimMan). In this

simulation, junior internal medicine residents had the opportunity to function as a team leader in a pre–cardiac arrest situation. We used debriefing to encourage reflective learning, mirroring the learning that occurs with difficult cases in real life.[6] Participants found the simulation session realistic and useful in improving both communication and collaboration.[13]

Effective use of simulation is a product of three components: training resources, trained educators, and curriculum integration. If any of these components is missing or deficient, the product will be ineffective.[14] Our program has access to the McMaster University Centre for Simulation Based Learning. The centre is equipped with many task trainers as well as state-of-the-art high-fidelity and moderate-fidelity mannequins. The Internal Medicine Program has also invested in task trainers that can be transported to different sites, making SBT more easily accessible for learners at various hospitals. A director of simulation position was created, followed by the development of a SIMS (simulation in internal medicine residency training) Committee that has faculty and resident representation. We are currently working toward having a fully integrated simulation curriculum, with graded complexity spread over 3 years of residency training.

It is our desire to recruit internal medicine programs across the country to collaborate in developing a national SBT curriculum. We are in the process of implementing a national environmental scan and needs assessment to determine the extent of SBT in internal medicine training programs. This will lead to the identification of common goals and objectives that can serve as the first step in the development of a peer-reviewed national curriculum. Open-source inventories, shared knowledge, and collaboration will facilitate the introduction of SBT in programs that do not have experienced simulation faculty. This will be more effectively facilitated with the support of national organizations such as the Canadian Society of Internal Medicine and RCPSC.

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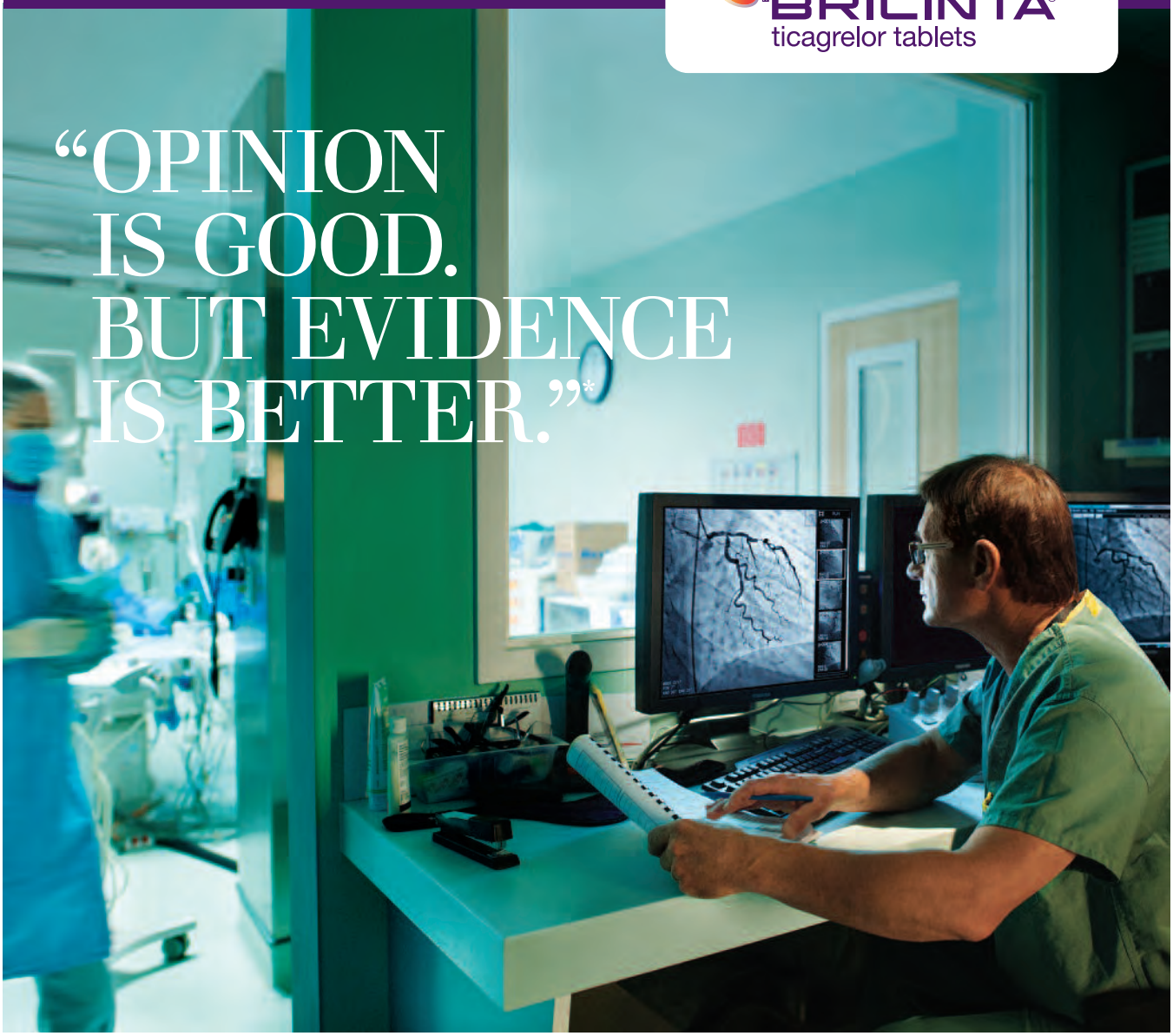

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What an Internist Needs to Know about Statistics

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The basics of medical statistics can be readily understood but are often approached by clinicians as if mysterious or forbidding. This may be because statistics was poorly taught at medical school or due to a tendency for articles on statistics to rapidly overcomplicate concepts. It is our hope that this series will be enlightening and provide a solid grounding in the building blocks to all evidence-based medicine.

This series is divided into the three main statistical areas: **descriptive statistics** as may be used commonly in audit projects, **inferential statistics** as may be used in therapeutic trials, and **diagnostic tests** in which sensitivity and specificity are important. Statistical concepts are illustrated with examples predominantly from the critical care literature. The choice of examples, however, should be regarded as non-significant when compared with any personal clinical practice. (There is no *p* value for this statement.)

In this article, we discuss concepts in descriptive statistics: types of data, measures of central tendency, measures of dispersion, and data distribution. Examine Table 1 and Table 2, an audit data set from a mixed neurological/general intensive care population. It is important to understand how the data are classified before you can interpret the numbers. This has been done for you in the tables. Data can be classified as categorical or numerical, and each of these two can be further subdivided into two subtypes (Figure 1).[1]

Table 1. Categorical Data from a Mixed Neurological/ General Intensive Care Unit Population

	n	%
Admissions	**1,036**	**100.0**
Male	617	59.6
Survival	825	79.6
Admission GCS (documented)	**609**	**100.0**
GCS 3–8	94	15.4
GCS 9–12	122	20.0
GCS 13–15	393	64.5

GCS = Glasgow Coma Score.

Categorical data are often non-numerical and consist of data grouped together. Where the groups, or categories, are nominated qualitatively the data are **nominal** (see Figure 1 for examples). There is no value judgment about the worth of each category in nominal data (e.g., being male is not inferior to being female). Nominal data categories are often mutually exclusive. For example, you cannot be both alive and dead.

Ordinal data are categorical data where there is a value judgment about the order of the categories. Scoring systems are common examples; they use numbers as labels for categories and to indicate order, and these numbers have no associated units. Two examples are the American Society of Anesthesiologists (ASA) Score and the Glasgow Coma Score (GCS). The higher the ASA Score or the lower the GCS, the worse the patient is, indicating order. The division between each category in ordinal data is not clearly mathematically defined. The ASA Score is assigned by patient history, whereas the GCS is defined by clinical examination. Neither relies on a mathematically measurable variable, nor can you apply simple mathematical analysis, such as multiplication or subtraction. This can be seen more clearly if we consider that it cannot be said that an ASA Score 4 patient is twice as sick as an ASA Score 2 patient. The ASA could have chosen colours (e.g., red for bad, green for good) instead of numbers for its grading system to describe the same ordinal data.

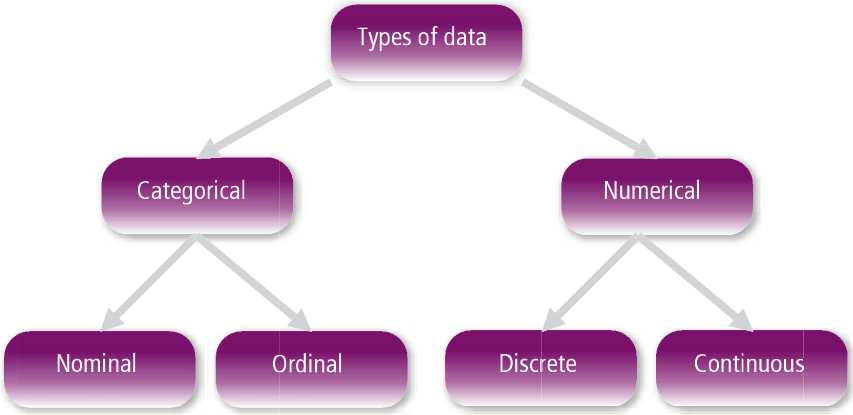
When categorical data are presented in a table, as in Table

Table 2. Numerical Data from a Mixed Neurological/General Intensive Care Unit Population

	Measures of Central Tendency			Measures of Dispersion			
	Mean	Median	Mode	Standard Deviation	Interquartile Range	Range	
						Minimum	Maximum
Age (y)	53.4	56	61	18.3	40–67	16	93
Length of stay (d)	5.7	3	2	6.0	2–7	1	52

1, it is best to give the absolute number or percentage occurring in each category. Occasionally, one sees an article calculating the **mean** or **median** for categorical data. Mean and median are measures of central tendency, which should be reserved for numerical data (Table 3). This is because you can't have a mean or median ethnicity (nominal), and you can't really have (although it is often spoken as if you can) a mean or median GCS (ordinal). But, for the patient cohort given in Table 1, we can tell you that the calculated mean, median, and mode for GCS is 12.3, 14, and 15, respectively. *Since it uses numbers, statistics allows you to calculate many things; you can, but you shouldn't.*

As we have seen above, in ordinal data each value has an uneven separation, and this makes the mean *meaningless* in this context. (A few outliers will skew the result dramatically; it relies on a detailed understanding of the GCS to interpret – a small difference in GCS may, for a patient, determine a large difference in outcome.) Better to present the data as percentages, as were given in Table 1; 15% of the admissions (where GCS was documented) have severe head injury, as defined by a GCS ≤8 at admission. The art of statistics is in presenting data appropriately and not in stirring the pot in the hope of generating interesting numbers.



Examples	Sex Mortality/ survival Diagnosis	GCS APACHE II ASA (scoring systems)	Number of admissions Lengths of stay	Age Mean arterial pressure PaO_2
Properties	Arbitrary, usually descriptive categories Has no units	Ordered (can be a number) categories Has no units	Usually an integer Has units Value can be counted	Usually a number, which can have a decimal point Has units Value can be measured
Advice	Give the number or percentage in each category	Give the number or percentage in each category Measures of central tendency or dispersion are not appropriate	Central tendency: median Dispersion: interquartile range Unless values are normally distributed	Central tendency: mean Dispersion: standard deviation Provided values are normally distributed
Charts	Bar chart Pie chart	Bar chart Pie chart	Histogram	Histogram

Figure 1. Types of data.

Table 3. Definition and Measures of Central Tendency

Term	Definition
Central tendency	The tendency for a set of values to gather around the middle of the set Generally measured by mean, median, and mode
Mean	Average $\sum^{x}/_{n}$ (sum of all values *[x]* over the number of values *[n]*) Should be applied to continuous data if normally distributed
Median	Middle value of an ordered sample of numerical values Extreme values do not affect the median as much as the mean, for example, length of stay, house prices Usually applied to numerical data (unless normally distributed)
Mode	Value that occurs most frequently Can be used for skewed numerical data or categorical data

Numerical data always involves numbers. Numerical data have order, units, and mathematical divisions between each value, allowing simple (and more complex) mathematical analysis. Numerical data are divided into discrete and continuous data (see Figure 1 for examples). **Discrete** data are the simplest form of numerical data. Typically, the values in discrete data have a regular mathematical division from the next (usually whole number data) and can be counted (e.g., the number of patients with ischemic heart disease).[2]

Continuous data are the most common type of data in medical settings and research. Continuous data are usually measured (e.g., with a measuring tape, Dinamap,

Table 4. Definition and Measures of Dispersion

Term	Definition
Dispersion	The spread of values
Range	Highest and lowest values Extreme or outlying values make unreliable Provides no information on variability of the values between the two extremes
Interquartile range	Is between the 25th and 75th centiles Is calculated by ordering all of the values and then excluding the bottom and top 25% of values (the vast majority of outliers) Used where the median is the appropriate measure of central tendency
Standard deviation (SD)	Used where the mean is the appropriate measure of central tendency Measure of variation about the mean = **square root of the sample variance**, where sample variance is the sum of the individual values (x) minus the sample mean squared, over the sample number (n) minus 1 $\sqrt{\Sigma (x - \text{Sample Mean})^2 / (n - 1)}$ In normally distributed data: • 68.27% of observations lie ± 1 SD about the sample mean • 95% of observations lie ± 1.96 SD about the sample mean • 99% of observations lie ± 2.58 SD about the sample mean

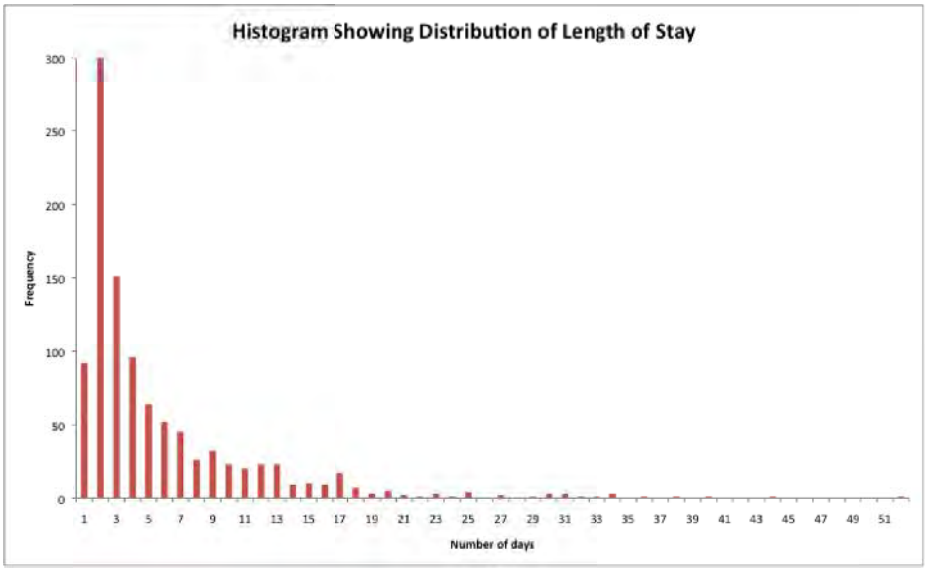


Figure 2. Example histogram from the data set used for Table 2.

thermometer), and there are a potential infinite number of values along a continuum depending on the accuracy of the measuring tool.[1,3]

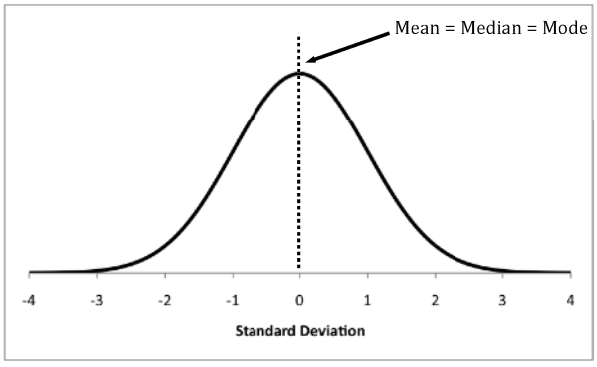
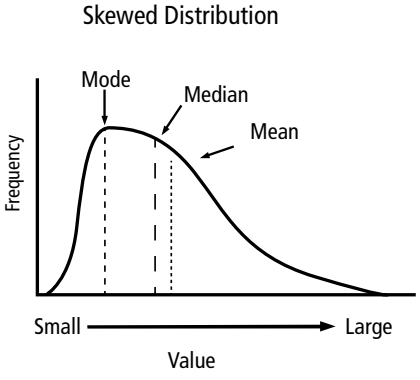
When numerical data are presented in a table, as was shown in Table 2, it is good to provide a measure of central tendency (see Table 3) and a measure of dispersion (Table 4). These measures help to describe the data and can provide more insight into the data. Table 2 gives three measures of central tendency and three measure of dispersion for age and length of stay. This is not typical and was given for example purposes only. Usually only the most appropriate measure is given. Typically, for discrete data, the *most appropriate* measures to describe the data are median and interquartile range, whereas for continuous data, mean and standard deviation are the most appropriate measures.

Numerical data can be summarized graphically in a histogram; this displays the frequency of a value occurring (y-axis) versus the value itself (x-axis) (Figure 2 shows an example using the same data set as Table 2). The difference between a histogram and a bar chart, which is used for graphically summarizing categorical data, is that in a bar chart the distance between each category on the x-axis is not of equal mathematical division. The shape of the histogram illustrates the way the data are distributed and gives guidance as to what sort of statistical technique may be appropriate to apply. If the data fit a "normal" Gaussian distribution, they are often continuous and mean and standard deviation are the appropriate measures to describe the data (Table 5).

The length-of-stay data shown in Figure 2 are skewed and do not fit a normal distribution. This is often the case in medical data sets, and there are a number of statistical options. Generally, it is often best to describe the data using median and interquartile range. Describing the data in this way is usually adequate for most audit and service evaluation investigations, and still allows for some statistical testing of significance if desired (to be described in a future article). Alternatively, statistical techniques exist to make non-normally distributed data more normally distributed (although this is not always appropriate).

Knowing what is appropriate is the art of statistics. There is no doubt that these distinctions and exceptions can be

Table 5. Data Distribution

Normal or Near-Normal Distributions	Non-normal Distributions
Many statistical techniques make assumptions being normal distributed. (although this is not always appropriate).	Statistical techniques exist to make non-normally about the data distributed data more normally distributed
Normal Gaussian Distribution	**Skewed Data Distribution**
	
• Symmetrical bell-shaped pattern • Many biological processes follow this pattern (e.g., height, weight) • Mean, median, and mode are equal	• Mean is toward the longer tail • Mode is toward the shorter tail • Median is between the mean and mode (Figure 2 data are skewed)

confusing. Benjamin Disraeli, a 19th century British prime minister, once said, "There are three kinds of lies – lies, damned lies and statistics." The key is to define the question you want answered and understand how the data were measured. In different circumstances, age, for example, may be continuous or discrete (whole years) or categorical (those less than 16 years categorized as children, those 16–25 as young adults, etc). Even in the simple calculations for length of stay in Table 2, it was first required to decide if an admission of less than 1 full day should be measured as 0 days or 1 day; this decision alters any statistical calculation (using hours instead of days would make the data more continuous but more complicated).

Statisticians have many tools at their disposal for transforming and describing data sets. For the rest of us, Figure 1 is a safe place to start.

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A Blueprint for Global Health Curriculum Development: The McMaster Internal Medicine Residency Program Experience

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Medical schools and residency programs are increasingly active within the realm of global health. Surveys suggest that most medical schools participate in global health–related activities, although the goals and scope vary widely.[1] Studies from Yale and Duke Universities showed that internal medicine residents who travelled abroad on a clinical elective gained knowledge in tropical medicine, tended to favour more general specialties, and worked more often with other marginalized populations.[2,3]

Existing global health curricula are driven largely by trainees, and residency programs will need to offer these activities to stay competitive and attractive. Furthermore, global health activities, at home and abroad, are well aligned with the CanMEDS health advocacy role, which calls for physicians to meet the needs of not only their own patients but also communities near and far. Given Canada's tradition of welcoming immigrants and refugees, the skills learned through a global health curriculum will be broadly applicable.

With these benefits in mind, we at McMaster University have started to envision an academic curriculum in global health for our Internal Medicine Residency Program. We have drawn on the important work of organizations such as the Canadian Pediatric Society (CPS), the Association of Faculties of Medicine of Canada (AFMC), the Global Health Education Consortium (GHEC), and the Working Group on Ethics Guidelines for Global Health Training (WEIGHT). Herein we present a blueprint for curriculum development, and a proposal for collaboration on a Canada-wide internal medicine residency curriculum in global health.

Step 1: Agreement on the Definition of Global Health

As a relatively new academic field, the concept of global health continues to evolve. Curriculum development therefore requires, as a first step, agreement on the definition of *global health*. In their 2009 article, "Towards a Common Definition of Global Health," Koplan et al. defined *global health* as "an area for study, research, and practice that places a priority on improving health and achieving equity in health for all people worldwide. Global health emphasizes transnational health issues, determinants, and solutions; involves many disciplines within and beyond the health sciences and promotes inter-disciplinary collaboration; and is a synthesis of population-based prevention with individual-level clinical care."[4]

This definition distinguishes the field of global health from both "public health" (which focuses more on the health of individual communities, with less emphasis on transnational determinants and solutions) and "international health" (which focuses more on the health issues of low- and middle-income countries and has been traditionally less multi-disciplinary). We

will use this definition as a starting point for our discussion.

Step 2: Development of a Consensus on the Core Competencies That a Global Health Curriculum Would Address

The next step is to define the educational goals and objectives of a global health curriculum. Several organizations have outlined core competencies in global health for undergraduate medicine programs. In addition, institutions in other jurisdictions, mostly in the United States, have developed and refined global health curricula specific to internal medicine residency programs. In Canada, CPS has endorsed a common global health curriculum to be used in all Canadian pediatric residency programs. Drawing from these various sources, an appropriate curriculum in global health for Canadian internal medicine residency programs can be developed.

In 2009, AFMC and GHEC published a joint proposal outlining core competencies in global health for undergraduate medical education.[5] This document provides a list of topics that should be included in any global health curriculum, and is summarized in Table 1.

In 2009, CPS developed a three-tiered approach to residency education in global health, categorizing knowledge and skills in global health as (1) those that every pediatric resident should acquire, (2) those tailored to residents with a specific interest in global health, and (3) those aimed at residents planning a career with a significant global health component. A common curriculum was agreed upon through national consensus meetings, and modules were developed that included PowerPoint presentations, videos, and possible objective structured clinical examination (OSCE) and written examination questions. This effort was supported by both CPS and the Royal College of Physicians and Surgeons of Canada.

At McMaster University, our global health curriculum committee, drawing on the work outlined above, has proposed a similar three-tiered framework of core competencies in global health for internal medicine residents. Within each of these tiers, learning objectives will be aligned with the topics included in the AFMC/GHEC proposal, and will be stratified according to the CanMEDS roles. In addition, enabling competencies will be developed within each domain. Our proposal provides both a framework for organizing curricular activities, and a mechanism for measuring the successes or failures of the program.

Step 3: Identification of Opportunities for Integration of Global Health Objectives into Internal Medicine Residency

Once consensus is reached on the content of a global health curriculum, efforts must then focus on how this material can be incorporated into the larger internal medicine residency curriculum (Table 2). Tier 1 learning objectives (those applicable to all graduating internal medicine residents) could be addressed through such traditional residency program activities as ward rounds, academic half-days, noon rounds, and periodic retreats. Elective rotations that focus on marginalized populations also could be developed. Resident knowledge and skills in global health could be tested using such formal evaluation tools as written examinations and OSCEs.

Tier 2 learning objectives (those tailored toward residents with special interest in global health) could be achieved through participation in such activities as a dedicated inter-disciplinary global health journal club, extracurricular courses on global health topics, research projects, and a mentorship program matching residents with faculty active in global health. Tier 3 learning objectives (for those wishing to have a significant

Table 1. Core Competencies in Global Health

Global burden of disease – including major causes of mortality and morbidity
Health implications of travel, migration, and displacement
Social and economic determinants of health
Population, resources, and environment – including effects of population growth and resource scarcity
Health care in low-resource settings
Human rights and health care

Table 2. Examples of Curricular Activities by Level of Interest

Tier 1
Academic half-day topics with global health focus
Dedicated monthly global health noon teaching on clinical teaching unit (CTU) rotations
Periodic global health program retreats
Objective structured clinical examination (OSCE) stations with focus on global health core competencies
Clinical electives that incorporate global health core competencies, for example with inner-city populations
Informal teaching on ward rounds
Tier 2
Dedicated global health journal club
Participation in extracurricular courses on global health topics
Development of research projects with appropriate faculty supervision
Formal global health mentorship program matching interested students to faculty active in this discipline
Tier 3
International electives with appropriate pre-departure and post-return training
Formal fellowship programs in global health for R4 year and beyond
Epidemiology training with focus on skills required for research in resource-limited settings

global health component to their career) would likely require the development of dedicated fellowships in global health within existing internal medicine residency programs. Such fellowships could be combined with a 4th year in general internal medicine, or added as a "clinical scholar" year, with appropriate funding. Participants would be expected to spend a significant amount of time in clinical global health activities, including both local experience with a focus on marginalized populations, and international placements.

Step 4: Implementation and Evaluation

A robust evaluation process will be required to ensure that the goals of a curriculum in global health are being met. With shortened resident work hours, benefits will need to be clearly documented in order to prove the worth of these activities. Documentation could take many forms, including testing formal knowledge on examinations, pre- and post-curricula surveys, and long-term evaluation of how training affects the careers of graduates. This will allow for constant re-evaluation and implementation of ideas for improvement. As well, any process that allows for travel abroad for the purpose of training or teaching should ensure that there is no negative impact on the host community, and ideally mutual benefit. Ongoing needs and impact assessments, as well as ethical surveillance, will be required.

Call to Action

The field of global health is rapidly expanding, both in scope and influence. Response to the increasing demand for learning in global health within traditional medical education programs has been varied and often haphazard. We therefore propose a collaborative effort to develop, implement, and evaluate a common global health curriculum across Canadian internal medicine residency programs.

While this curriculum will draw on the strengths of similar efforts in related specialties, it will also provide innovation by focusing on the needs of internal medicine residency and incorporating both key and enabling competencies. The benefits of such collaboration would include the following:

- Building consensus on the core competencies in global health that all internal medicine residents in Canadian programs should acquire prior to licensure, building and expanding upon previously accepted undergraduate core competencies
- Pooling of expertise, including global health theory and practice, curriculum development, and curriculum evaluation
- Sharing of and rationalizing use of resources (e.g., teaching modules and postgraduate courses), including collaborations with institutions in low- and middle-income countries
- Strengthening and sustaining a sense of community among Canadian general internists and subspecialists with an interest in global health
- Strengthening links to other postgraduate disciplines with an interest in global health

As a next step, we are undertaking a survey of all Canadian internal medicine residency programs, to document current activities and perceived needs in global health education within each of these programs. We will also solicit input from each program for representatives for a new national committee whose goal will be to provide a proposed curriculum in time for the October 2013 meeting of the Canadian Society of Internal Medicine.

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Disseminated Herpes Zoster in an Apparently Healthy Middle-Aged Woman

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About the Authors

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Herpes zoster is a characteristic dermatomal maculovesicular rash that results from reactivation of varicella-zoster virus (VZV). Dissemination, or widespread distribution of vesicular lesions beyond the limits of the primarily involved dermatome, occurs almost exclusively in individuals with severe underlying immunodeficiency, such as malignancy, human immunodeficiency virus, and advanced age. Waning cell-mediated immunity is thought to be the final common pathway permitting reactivation and dissemination. Here, however, we present a case of disseminated herpes zoster (DHZ) that occurred in an apparently immunocompetent patient without any traditional risk factors.

Case

Upon returning from a vacation in Palm Springs, California, a 58-year-old white female presented to the emergency department (ED) with a 5-day history of headache and progressive pain, redness, and rash over her right forehead and eyelid. Pain was the initial manifestation, with small vesicles then appearing at her hairline and progressing caudally to involve the eyelid (Figure 1). In addition to significant periorbital edema, she reported a "burning" sensation in her right eye. While still on vacation, on the day prior to her presentation, she had presented to an ED and was given a prescription for acyclovir 800 mg PO five times daily. This patient suffered from hypertension, hypercholesterolemia, a longstanding peripheral sensory neuropathy that had not yet been diagnosed, and chronic ethanol abuse (one bottle of wine per day for at least 10 years) and had a previous 60 pack-year smoking history. She had no known history of immunodeficiency or malignancy. Her medications included a perindopril/indapamide combination tablet and the recently prescribed acyclovir. She reported an allergy to penicillin, the nature of which was unclear.

On examination, she was febrile, with a temperature of 38.4°C; the remainder of her vital signs were within normal limits. An exquisitely tender, erythematous, papulovesicular rash covered her right forehead and eyelid but spared the tip of her nose and did not cross the midline. She had significant periorbital and eyelid edema, effectively closing her right eye. She had jolt accentuation of her headache but no other signs of meningismus. On her torso, back, right arm, and right upper thigh, she had multiple (>30) small erythematous, non-tender

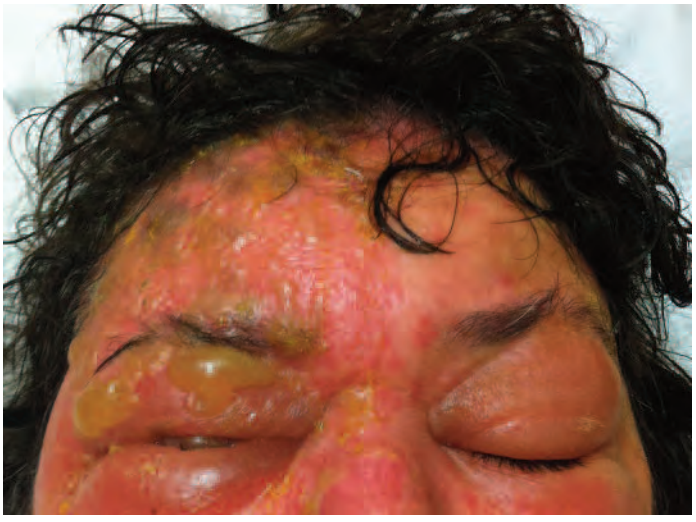

Figure 1. Periorbital distribution of herpes zoster.

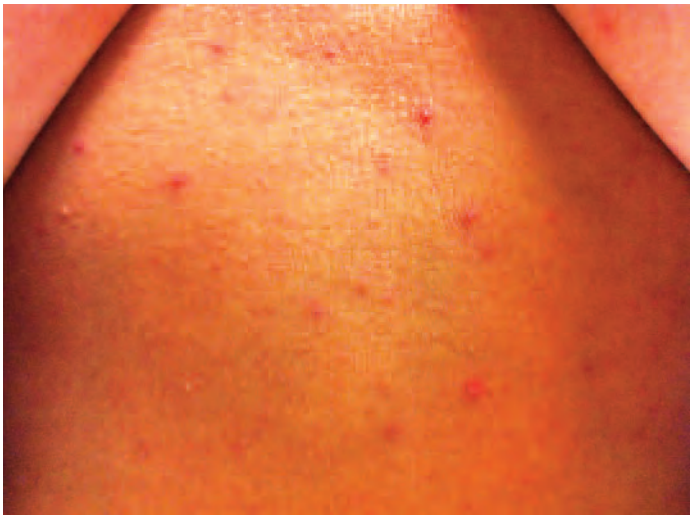

Figure 2. Disseminated vesicular lesions on torso and epigastrium.

papules, some of which were vesicular (Figure 2). The remainder of her physical examination was normal.

Initial laboratory results showed a mean corpuscular volume (MCV) of 104 fL (normal 82–100 fL), a platelet count of 113 × 10^9/L (normal 150–400 × 10^9/L), a γ-glutamyltransferase (GGT) level of 273 U/L (normal 8–35 U/L), an alanine transaminase (ALT) level of 50 U/L (normal 1–40 U/L), and an aspartate transaminase (AST) level of 75 U/L (normal 8–32 U/L). An unenhanced computed tomography scan of the head revealed stranding in the subcutaneous tissue of the V1 distribution of the trigeminal nerve, but no intracranial abnormalities. Cerebrospinal fluid (CSF) analysis revealed a white blood cell count (WBC) of 12.2 × 10^6 (0.0–5.0 × 10^6), composed of 6% neutrophils, 65% lymphocytes, and 29% monocytes; and a protein level of 0.6 g/L (0.15–0.45 g/L), with a normal glucose level and no xanthochromia.

Based upon the characteristic appearance and widespread, multi-dermatomal location of the papulovesicular lesions, a clinical diagnosis of DHZ was made. The patient was admitted to the internal medicine service for IV acyclovir therapy and to complete laboratory investigations for occult malignancy and other immunodeficiency.

The clinical diagnosis of DHZ was confirmed by the identification of VZV direct fluorescence antigen positivity in her CSF and fluid from a swab of a torso vesicle. A screen for underlying immunodeficiency was then undertaken. Serologic tests for human immunodeficiency virus (HIV) 1 and 2, hepatitis A, B, and C, and syphilis were negative. However, flow cytometry revealed a mild decrease in the total number of T cells at 0.680 × 10^9/L (normal 0.800–2.531 × 10^9/L), and in the CD4 fraction in particular, at 0.371 × 10^9/L (normal 0.499–0.651 × 10^9/L). In addition, serum protein electrophoresis; C-reactive protein (CRP); C3 and C4; IgA, IgG, and IgM; anti-smooth muscle, anti-mitochondrial, and anti-nuclear antibody screens were all within normal limits. Blood and CSF cultures were negative, as were CSF studies for enterovirus RNA and herpes simplex virus DNA. Abdominal ultrasonography revealed fatty infiltration of the liver and a mildly enlarged spleen (13.4 cm).

She was treated with 14 days of acyclovir 500 mg IV q8h. At the recommendation of the ophthalmology service, she also received a 9-day course of 1% trifluridine eye drops five times a day, and a 7-day course of 1% prednisolone eye drops. With the resolution of her periorbital edema, a complete ophthalmologic examination was performed and was normal. There was concern regarding a superimposed bacterial cellulitis, and she was treated with ceftriaxone 1 g IV q24h for 9 days.

By the 5th post-admission day, all of the patient's lesions had crusted over. Unfortunately, she developed diarrhea due to *Clostridium difficile* enteritis, and a 14-day course of oral metronidazole was prescribed. At the time of discharge, the patient was feeling well and the crusts of most of her lesions had sloughed off.

Discussion

The characteristic rash of herpes zoster results from the reactivation of latent VZV. During the primary infection with the virus, which manifests as varicella or "chicken pox," the virus infects peripheral sensory nerves and migrates centripetally, ultimately reaching the dorsal root ganglia.[1] Varicella-zoster-specific cell-mediated immunity (CMI) keeps the virus in a dormant state. As CMI wanes, as a result of aging, malignancy, and immunosuppressive drugs, VZV is permitted to reactivate, resulting in the painful, papulovesicular rash characteristic of herpes zoster.[1] Indeed, whereas the incidence of herpes zoster in the general population is approximately 1.3/1,000 patient-years,[2] it is >10/1,000 patient-years and 29/1,000 patient-years in those over 80 years of age[1] and in those with HIV,[3] respectively.

Herpes zoster is classically restricted to a single dermatome. However, the involvement of discrete lesions removed from the primary dermatome are commonly reported,[1,4] occurring in 29 of 88 (29%) patients without known malignancy in one prospective series.[5] These ectopic lesions are hypothesized to result from hematogenous seeding.[1] At some critical threshold, the number of these ectopic lesions heralds frank dissemination, a characteristic that has both therapeutic and prognostic significance. Three distinct distributions of herpes zoster have been reported: the classic localized, monodermatomal herpes zoster; herpes zoster with aberrant lesions; and frank dissemination.[4] Unfortunately, dissemination has not been clearly defined in the literature. Of the few studies that report a definition, thresholds range from 10 to 30 lesions.[1,4] In the absence of any physiological data or rationale, these disparate definitions appear arbitrary.

For dissemination to occur, significant immunocompromise is thought to be necessary. Decline in VZV-specific T-cell function is the final common pathway thought to be necessary to allow reactivation. This decline is most often mediated by increasing age but is also characteristic of T-cell-compromising states such as those resulting from HIV, malignancy, and immuno-suppressive therapies. Dissemination occurs in approximately 2% of population-based and prospective studies of general in-patients with herpes zoster.[3] Unfortunately, these studies did not report their definition or threshold for "dissemination," nor did they report the immune status of the affected patients.

DHZ in apparently immunocompetent, non-elderly patients

is extremely rare, being limited to three case reports.[7–9] A review of older cohort studies, with questionable or unstated definitions of dissemination and often unclear or absent assessments for immunocompromise, may yield several more cases.[4,10]

There are no specific guidelines to direct treatment or investigation for occult immunocompromise in patients with DHZ. However, given the degree of immunosuppression implied with dissemination, investigation seems appropriate in these patients.

We present a case of DHZ in an apparently immunocompetent patient. In the absence of known immunodeficiency, a predisposing condition, or advanced age, we propose that ethanol abuse, with a subsequent impact on CMI, may have allowed for the reactivation and dissemination of herpes zoster. There is clear in vitro and in vivo evidence that chronic alcohol consumption impairs cell-mediated immune function. Chronic ethanol use reduces T-cell number[11] and function, which translates into significant increases in infection rates. This effect is thought to be mediated by a combination of ethanol-induced apoptosis and interference with cytokine-mediated T-cell production.[11] Although ethanol abuse has been demonstrated to increase the incidence, and alter the course of, a number of viral infections, including hepatitis C and HIV,[11] only a single study comments on effect of ethanol on VZV reactivation.

In a Brazilian case-control study[12] that sought to determine historical factors that triggered non-DHZ, there was a significantly greater frequency of ethanol consumption in the herpes zoster group (12/30 patients; 40%) as compared with the control group (14/100 patients; 14%). These authors concluded that ethanol consumption may be a factor in triggering herpes zoster. Unfortunately, ethanol consumption was not quantified, nor was it qualified (e.g., as "abuse" or "heavy").

In conclusion, we present a case of DHZ in an apparently healthy 58-year-old woman. In such apparently healthy patients with DHZ, investigation for occult malignancy and HIV is recommended. If this evaluation ultimately proves to be negative, ethanol abuse should be considered.

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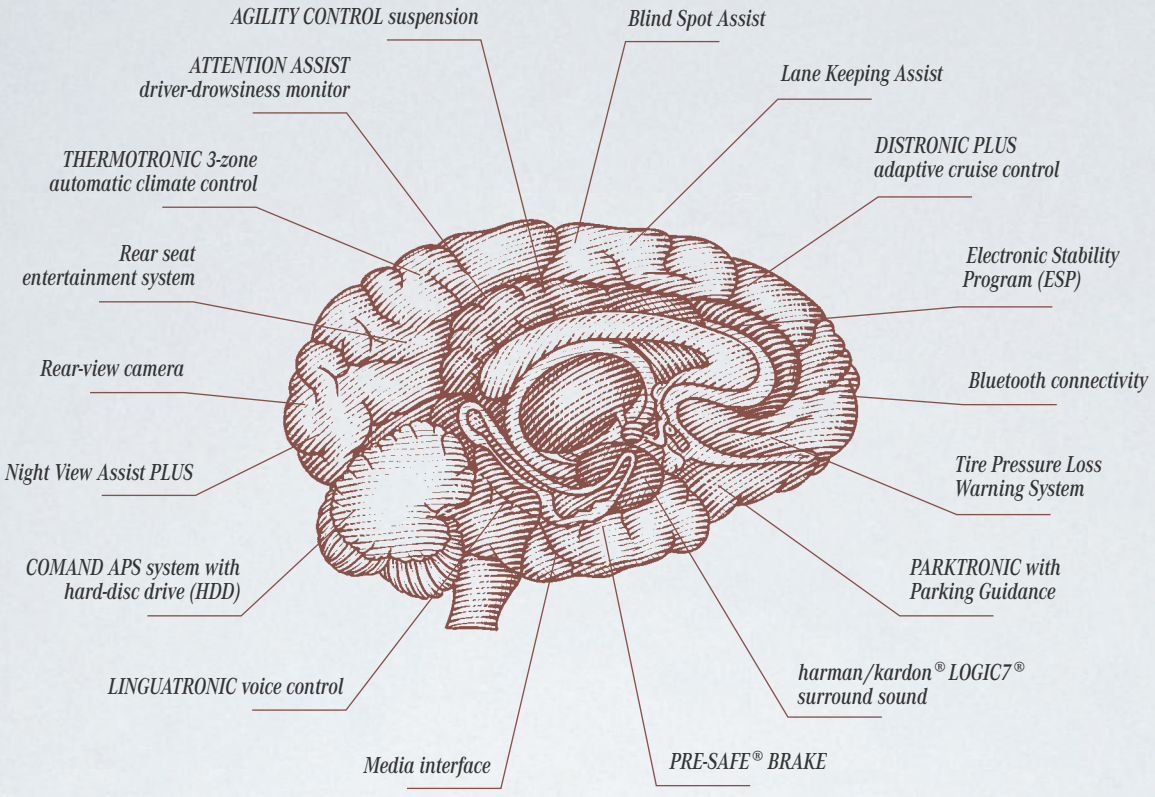

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Hydrophobia Associated with Severe Hypernatremia, Acute Kidney Injury, and Rhabdomyolysis

Mohammed Almaani MD, Raymond Kao MD

About the Authors
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Case

A 33-year-old male was brought to the emergency department (ED) by his family with a 10-day history of decreased to no oral intake and a progressive unsteady gait. He had a known history of major depressive disorder, agoraphobia, acrophobia, and hydrophobia, which had not been treated with any medications; he had been followed up by outpatient psychiatry.

On arrival at the ED, he was noted to be drowsy, with a Glasgow Coma Score (GCS) of 14/15 (E4, V4, M6), blood pressure of 85/40 mm Hg, heart rate of 140 beats/minute, temperature of 38.5°C, respiratory rate of 38 breaths/minute, and oxygen saturation at 95% on room air. He was noted to be severely dehydrated with dry mucous membranes, a flat jugular venous pressure, mottled skin, and anuria. He was resuscitated in the ED with 4 L of intravenous normal saline over 4 hours and started on empiric intravenous antibiotics, piperacillin-tazobactam 4.5 g IV q6h, for presumptive septic shock.

The initial laboratory examination revealed the following: a serum sodium level of 210 mmol/L, potassium level of 5 mmol/L, chloride level of 165 mmol/L, bicarbonate level of 22 mmol/L, blood urea nitrogen (BUN) at 37.1 mmol/L, serum creatinine at 922 µmol/L, serum osmolality at 459 mOsm/L, creatinine kinase (CK) at 13,600 U/L, white blood cell count of 18×10^9/L, hemoglobin level of 20 g/L, platelets at 85×10^9/L, hematocrit of 0.61, lactate at 8.7 mmol/L, aspartate transaminase (AST) level of 536 U/L, lipase level of 264 U/L, serum amylase level of 248 U/L, serum albumin at 57 g/L, and total bilirubin at 20 µmol/L. The screenings for toxic drugs and substances upon admission were negative, and the initial chest radiograph and computed tomography (CT) of the head were normal. The patient was transferred to the intensive care unit (ICU) for continuing fluid resuscitation and hemodynamic monitoring. After the initial normal saline bolus, infusions at 200 cc/h were performed to treat the ongoing dehydration and severe hypernatremia. His serum sodium was monitored closely every 2 hours; the goal was to lower it by 10–15 mmol/L over 24 hours (Figure 1).

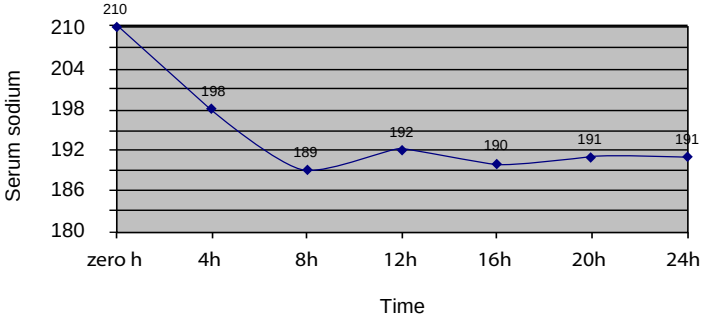

Figure 1. Serum sodium (mmol/L) in the first 24 hours of admission.

At 24 hours' post-admission, our patient's serum sodium levelled to 191 mmol/L. The intravenous fluid was switched to half normal saline at 200 cc/h, coupled with an infusion of free water through a nasogastric tube at a rate of 120 cc/h. At 48 hours' post-admission, his serum sodium had improved to 169 mmol/L (Figure 2). On day 3 of his admission, it was noted that his serum creatinine and CK continued to climb, reaching 1,136 µmol/L and >22,500 U/L, respectively (Figure 3 and 4). He continued to be anuric, with a total cumulative fluid balance of >12 L since admission. Hemodialysis (HD) was initiated for worsening of acute kidney injury and CK level; he was also intubated for mechanical ventilation to protect his airway from increasing somnolence due to worsening uremia (Figure 5).

A repeat CT of the head did not reveal any abnormality. A sub-hairline electroencephalogram was also performed, and it did not reveal any seizure activities. Our patient received HD

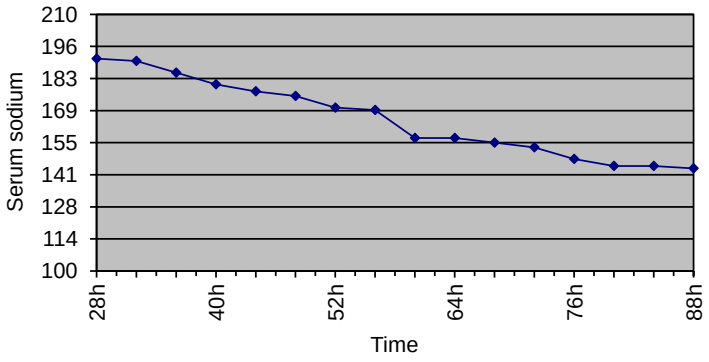

Figure 2. Serum sodium (mmol/L) from day 2 to day 4 of admission.

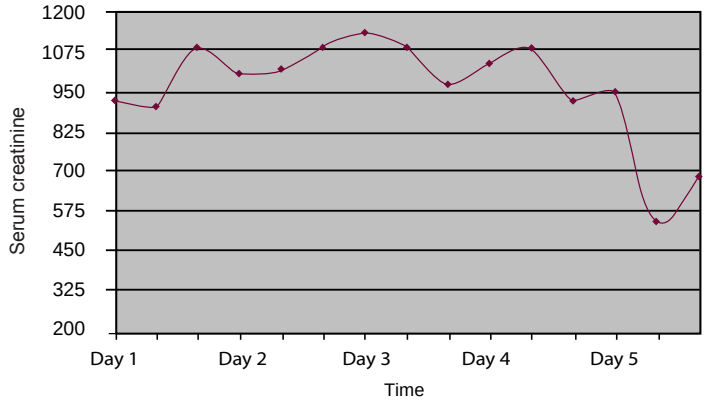

Figure 3. Serum creatinine (μmol/L) from day 1 to day 5 of admission.

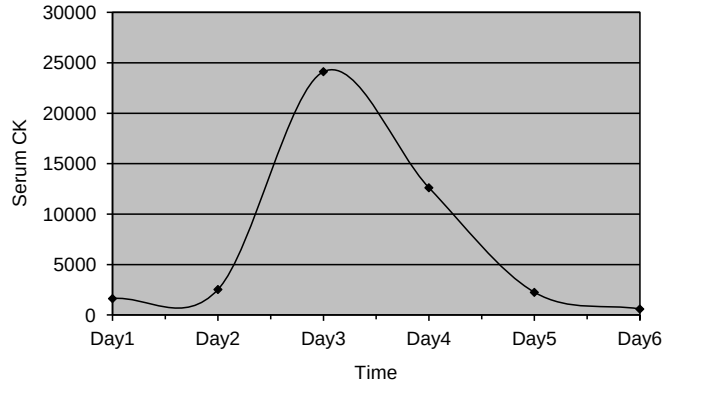

Figure 4. Serum creatinine kinase (U/L) from day 1 to day 6 of admission.

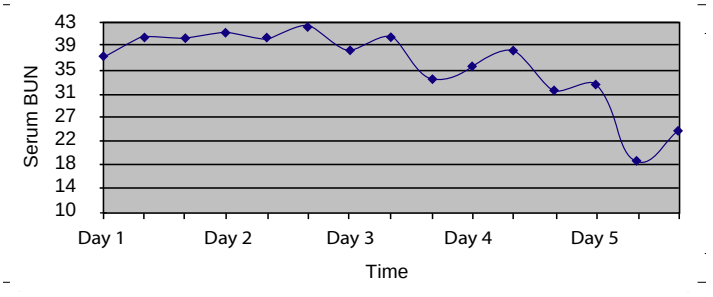

Figure 5. Serum blood urea nitrogen (BUN) (mmol/L) from day 1 to day 5 of admission.

daily for 3 days; he was then switched to continuous veno-venous hemodialysis (CVVHD) due to persistent hypotension secondary to presumptive worsening sepsis. His initial blood culture in the ED was negative, but the sputum culture was positive for *Enterobacter aerogenes*, which was resistant to piperacillin-tazobactam; subsequently, his antibiotics were changed to imipenem 500 mg IV q6h. He was switched back to intermittent hemodialysis on day 7 of his admission to the ICU when he became hemodynamically stable. His serum sodium, CK, and neurological status continued to improve, and he was extubated on day 15 of admission to the ICU. He was discharged home under his family's care after a 1-month hospital stay.

Discussion

Hypernatremia is a relatively uncommon cause of ICU admission, and includes only 2% of the admitted patients.[1] This is because thirst, one of the most powerful human behavioural drives, which is regulated by serum osmolality through the control feedback loop of antidiuretic hormone (ADH), spurs a person to seek out and drink water.[2–4] When thirst is maximally stimulated in human beings, the craving for water cannot be ignored, and it can become sufficiently intense to dominate all other thoughts and sensations.

There are only four reported cases of a psychiatric patient presenting with hypernatremia,[1–4] and none of the cases required ICU admission and renal replacement therapy. Here we report the first case of severe hypernatremia due to hydrophobia that required ICU admission and that was complicated by rhabdomyolysis and acute kidney injury.

Hypernatremia can result from administration of hypertonic sodium solutions, but it occurs more commonly due to a loss of free water in patients such as sick infants, the elderly, and adults with limited access to water, impaired mental status, or an abnormal thirst drive. Thirst is one of the most powerful behavioural drives that can be experienced by human beings.[5,6] The threshold for thirst sensation varies widely among healthy individuals, but it usually occurs at a serum plasma osmolality of approximately 290 mOsm/kg. Above this threshold, the thirst sensation increases rapidly, and it becomes significantly intensified at serum plasma osmolalities of 300–305 mOsm/kg. To overcome this strong thirst drive sensation sufficiently to result in a severe metabolic abnormality such as hypernatremia, a significant anatomical or psychogenic disturbance is required. This is usually seen in adults who have a pathological process involving the destruction of the hypothalamus or supraoptico-hypophyseal system. But psychogenic oligodipsia is not only an extremely rare condition, it is an even less common presentation of the

hyperosmolar syndrome, which can often go unrecognized in some psychiatric patients.[1] Psychogenic polydipsia with hyponatremia is a well-documented condition in psychiatric patients,[7,8] but there are only four reported cases of psychogenic adipsia leading to hypernatremia requiring medical managment.[1] None of reported cases was complicated by rhabdomyolysis and acute kidney injury requiring renal replacement therapy.

Rhabdomyolysis due to hypernatremia and hyperosmolality is a rare complication,[9] and its mechanism is unknown. Grinstein et al.[10] suggested that during the shrinkage of the cells in the hypertonic medium, the normal cell volume is kept by means of an Na+/H+ antiport and Cl−/HCO3− exchange at the level of the cell membrane. However, in many cell types, the activation of the antiport is also mediated by an increase in intracellular calcium. After a significant serum hypertonic stress, the intracellular calcium will reach a maximum level in 6–8 minutes and give rise to the activation of protein kinases and result in cell lysis. Due to this cell lysis, muscle enzymes are liberated and rhabdomyolysis develops. Evidence for a direct causal link between hypernatremia and rhabdomyolysis is provided by three reported cases of central diabetes insipidus resulting in severe hypernatremia and rhabdomyolysis in the absence of other potential causes.[11–13] In all cases, the serum sodium concentration was >180 mmol/L. Abramovici and colleagues, reporting a case series of 18 patients with hypernatremia, showed a significant linear correlation between serum sodium concentration and serum CK level.[9]

Conclusion

Our patient suffered from a psychiatric illness involving severe water phobia that interfered with his thirst drive and led to severe hypernatremia. This resulted in a worsening neurological status followed by rhabdomyolysis and acute kidney injury, which required ICU admission and renal replacement therapy. This case provides evidence that hypodipsia or adipsia from psychiatric disturbances causing severe hypernatremia can occur and is potentially reversible.

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Reflections on Dr. Allan D. Cohen

Donald Farquhar MD SM

About the Author

Donald Farquhar is the editor of Canadian Journal of General Internal Medicine*, and is a professor of medicine in the Schulich School of Medicine, Western University, in London, Ontario. He is a former assistant professor of medicine at Dalhousie University, in Halifax, Nova Scotia (1989–1992). Correspondence may be directed to Donald.Farquhar@sjhc.london.on.ca.*

Dr. Allan D. Cohen with his wife, Annalee.

Allan Cohen was one of the first faculty colleagues I got to know when I joined the Department of Medicine at Dalhousie as an assistant professor in 1989.

Although my family's roots were in Nova Scotia, I had grown up and completed my medical residency and fellowship training in London, Ontario, and so I had come to Dal "from away," as Maritimers say. Everything and everyone about the Department of Medicine – except its then head, Dr. George Carruthers, who, like me was also an expatriate Londoner, and had recruited me – were new. For the first few weeks, I confess that I felt like a "fish out of water."

Allan quickly made himself known to me, and with his warmth, friendliness, and deep interest in people – particularly young people – he made me feel not only welcome, but special. And so my memories of Allan are among the most precious things I carry with me from my 3 years on faculty at Dal. What I remember most about him are his enthusiasm, his helpfulness, and his unfailingly good cheer.

In those days, Allan, I believe, was in his mid- to late forties and was already a full professor and head of Dalhousie's Division of Nephrology. I soon learned that in the professional realm, he was an exceedingly accomplished individual, held in high regard by his colleagues both locally and across North America. I also learned that he had been a brilliant student, and, if I'm not mistaken, the gold medallist in his medical school class at Dalhousie.

I learned none of this from Allan himself, of course. Among his many gifts of heart and mind was a certain humility that added to his charm. Allan was always more concerned about others than about himself. And that wide circle of concern encompassed his students, residents, colleagues, family, and, most of all, patients.

My duties as a member of the attending staff of the Victoria General Hospital in Halifax included serving as attending physician in the Medical Intensive Care Unit (MICU) for 2 or 3 months of the year. How well I remember a week when all five of our critically ill, mechanically ventilated patients were suffering from acute renal failure, either as their primary problem or as a complication of the illness that had brought them to us. Allan Cohen was the on-call nephrology consultant at the time, and so was intimately involved in the care of each of those patients.

During that week, we spent so much time interacting with Al – and learning from his clinical wisdom, judgment, and humanity – that it started to feel as if he were a full-fledged member of our MICU team. After a few days, we got it into our heads that we should somehow acknowledge this formally by awarding Al with a mock "certificate of membership" in the MICU staff. One of our residents was adept at computers and, with the help of the old "Harvard Graphics" program, was able to produce a very official looking document, which we all dutifully signed.

When we presented Al with his MICU membership certificate at the end of the week, he seemed, for a moment, at a loss for words. This of course was very unusual for him. But we all smiled and laughed and took pleasure in the moment. And that was that – or so it seemed.

A few weeks later, when we were both off-service, I had occasion to drop by Al's office for one of our many informal talks. As we chatted, I looked admiringly at the many framed diplomas, fellowship certificates, and awards of merit mounted on the wall behind Al's desk. Imagine my surprise when my gaze came to rest on our MICU membership certificate, handsomely framed and taking its place among seemingly countless other honours!

I have thought about that moment many times since then. Seeing our made-up mock diploma mounted on Al's office wall said to me that he had been touched in some way by what we had considered at the time to be just another bit of hospital silliness. Now I believe in retrospect that our team's gesture that day was more than just silliness. Presenting Al with his honorary MICU membership certificate was, in fact, an expression of our deep affection and respect for him as a colleague and friend. For all his humility, Al sensed this perhaps better than we did, and it is now clear to me that our silly certificate meant something to him. Without necessarily knowing it, I think that, in some small measure, we had repaid him for all that he had given to us and to our patients.

I remember how empty and sad I felt when I learned of Al's untimely sudden cardiac death, a year or two after I had moved on from Dalhousie. I had lost an esteemed colleague, trusted mentor, and good friend. The poet Galway Kinnell once wrote, "If love had not smiled, we would never grieve." In and through Allan Cohen's life, love smiled with great warmth, generosity, and grace!

Dr. Norm Campbell, professor of medicine and community health sciences at the University of Calgary, and a CIHR chair in hypertension prevention and control at the Libin Cardiovascular Institute of Alberta, has been named by Hypertension Canada as the 2012 recipient of the J. G. Fodor Award, in recognition of his efforts to prevent and control hypertension in Canada. Norm, a former chief of the University of Calgary's Section of General Internal Medicine, is well known in the Canadian GIM and clinical pharmacology communities, and is a former president of both the Canadian Hypertension Society and Canadian Society for Clinical Pharmacology. Norm's academic and advocacy activities in recent years have focused on dietary salt, and he has been selected to chair a Technical Advisory Group on Cardiovascular Disease Prevention through Dietary Salt Control Policies and Interventions, for the Pan American Health Organization.

Dr. Kaberi Dasgupta, associate professor of medicine in the Divisions of Internal Medicine and Endocrinology at McGill University, has been awarded a New Investigator Career Award by the Canadian Institutes of Health Research. Also a scientist in the Division of Clinical Epidemiology at the Montreal General Hospital, Kaberi completed her MSc in epidemiology at McGill in 1999, while practising as a community-based general internist in Amos in northwestern Quebec! Her research focuses on the prevention of cardiovascular disease in patients with type 2 diabetes and other conditions of insulin resistance. Kaberi has recently been successful in obtaining substantial operating and/or catalyst grants to support her research from the Canadian Diabetes Association, the Heart and Stroke Foundation of Canada, and the Canadian Institutes of Health Research!

Dr. Kathryn Myers, professor of medicine in the Schulich School of Medicine at Western University, and a core researcher at Western's Centre for Educational Research and Innovation (CERI), has been awarded the "Best Paper" prize for her presentation at the 2011 AAMC-RIME (Research in Medical Education) meeting in Denver. Kathy's presentation, "A mixed-methods analysis of residents' written comments regarding their clinical supervisors," will be published as an article in the October 2012 edition of *Academic Medicine*, 87(10), titled "Engaged at the Extremes: Residents' Perspectives on Clinical Teaching Assessment." Co-authors of the paper are Elaine Zibrowski and Dr. Lorelei Lingard, also with the CERI. Kathy practises general internal medicine in the London teaching hospitals, and is chair/chief of Western's Division of General Internal Medicine.

Dr. Alexandro Zarruk, a PGY4 resident in the Department of Medicine at the University of Ottawa, was recently presented with the Ottawa Hospital Foundation's Guardian Angel award, by Ottawa Hospital CEO Dr. Jack Kitts, at a reception attended by family, friends, and colleagues. The Guardian Angel award recognizes a health professional who is nominated by a patient for exceptional care and kindness above and beyond the call of duty. Well done, Alexandro!

CSIM Mission Statement

Mission Statement
The CSIM is a non-profit professional society that promotes the health and well being of Canadian patients, their communities, and their health care systems. We seek to foster leadership and excellence in the practice of General Internal Medicine (GIM) through research, education, and advocacy for health promotion and disease management.

Vision
We believe that General Internal Medicine in Canada plays a central role in the training of current and future clinicians, in clinical research, in patient care, in health promotion, and in health advocacy; and that it unites a body of knowledge, values, and principles of care that lay the foundation for excellence in the Canadian health care system.

Values
We embrace the ethical and professional standards that are common to all healing professions, as well as the specific values of generalism, teamwork, competency-based training, life-long learning, evidence-based medicine, holism, and humane, patient-centered care.

Mission
La Société canadienne de médecine interne (SCMI) est une association professionnelle sans but lucratif qui entend promouvoir la santé et le bien-être des patients, des collectivités et des systèmes de santé canadiens. Elle souhaite également promouvoir le leadership et l'excellence dans l'exercice de la médecine interne générale en favorisant la recherche, l'éducation, la promotion de la santé et la gestion des soins thérapeutiques.

Vision
La Société a l'intime conviction que la médecine interne générale occupe une place centrale dans la formation des cliniciens aujourd'hui et à l'avenir, dans la recherche clinique, dans la prestation des soins et des services de santé et dans la promotion de la santé, et que la discipline se fonde sur un savoir, des valeurs et des principes thérapeutiques essentiels à la poursuite de l'excellence dans le système de santé canadien.

Valeurs
La Société fait sienne les normes éthiques et professionnelles communes aux professions de la santé ainsi que les valeurs particulières du généralisme, du travail d'équipe, de la formation axée sur les compétences, de l'éducation permanente, de la médecine factuelle, de l'holisme et des soins et des services de santé humains, centrés sur le patient.

CSIM Continuing Professional Development Mission Statement

Our ultimate goal is to go beyond the simple transmission of information. Our goal is to make a lasting impact on the knowledge, skills and attitudes of clinicians and future clinicians; to narrow the theory to practice gap; to improve the health of our patients and of all Canadians.

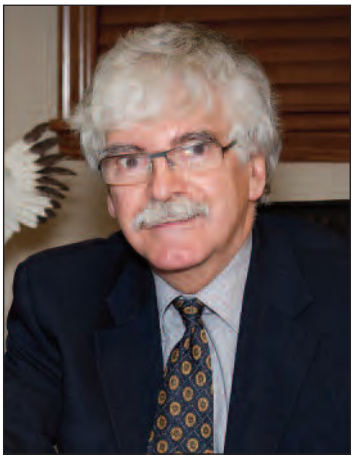
Mission de la SCMI sur le plan du développement professionnel continu

Notre but ultime déborde du cadre de la simple transmission d'information. Il consiste à produire un effet durable sur le savoir, les compétences et les attitudes du médecin, à combler l'écart qui sépare la théorie de la pratique, à améliorer la santé de nos patients et de tous les Canadiens.

Osler Award Winners 2012

Dr. Bill Coke trained at McGill University, the Mayo Clinic, and the University of Manitoba. He was program director for GIM in Winnipeg, Ottawa, and Edmonton, before moving to Toronto, where has been instrumental in building and directing a Hospital Medicine Fellowship Program and representing hospitalists at the OMA. He is known to CSIM and RCPSC members for his participation at many levels in professional development and standards. He is chair of the College Internal Medicine Specialty Training Committee and has been on many residency accreditation committees. Bill's advocacy for GIM as a specialty in its own right was rewarded last year, and now he is helping design the 2nd-year experience at the University of Toronto.

Bill is known as an excellent clinical teacher and has been recognized with several awards. He is a planner with a remarkable background in the profession, a doer, and well respected by his colleagues. He has worked tirelessly to bring innovation to patient care, in ambulatory and ward settings, and has led by example, hard work, and dedication. He has been compared to Osler's descriptor of the physician: "A studious hard-working man who wishes to know his profession thoroughly, who lives in the hospitals … and strives to obtain a wide and philosophical conception of disease and its processes … [and] form[s] the bulwarks of our ranks."



Dr. Rene Roux trained at Sherbrooke and entered practice at the Hôpital Sainte-Croix. He has consulted at the Trois-Rivières hospital, in Quebec, where he played a major role in opening the first IM teaching unit. In 1976, he established the GIM training program in Drummondville, Quebec, one that has become a model for community-based GIM. He is a strong proponent of the role of the multifaceted generalist within the medical profession, and with government too. He has helped establish funds to aid residents in acquiring the procedural skills necessary to function within rural practice. He is a builder, who has rallied around him a dynamic team committed to research and education.

Rene has been president of ASMIQ and still plays a prominent role on their executive. For over 30 years, he has worked tirelessly to promote generalism, in his workplace and for his province. Not surprisingly, his commitment, clinical excellence, and leadership have been an inspiration to generations of young residents who have adopted him as their mentor and continue to seek his guidance.

Abstracts from the 2012 Annual Meeting

Oral Research Sessions

"Peri-operative Anti-TNF Treatment and Post-operative Complications in Patients with Crohn's Disease: A Systematic Review and Meta-Analysis" – *Dr. Neeraj Narula, McMaster University*

"Impact of Local Low Cost Rapid Response Team in a Canadian Tertiary Care Hospital" – *Dr. Andrea Blotsky, McGill University*

"Advance Directives: Prevalence and Attitudes of Advanced Cancer Patients Receiving Chemotherapy, A Single Institution Study" – *Dr. Jeanne du Manoir, University of Toronto*

"Adverse Events during Aliskiren Use among Patients Receiving Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers" – *Dr. Cameron Gilbert, University of Toronto*

"Preoperative Hyponatremia and Perioperative Complications" – *Dr. Alexander Leung, Harvard Medical School*

"Predictability of Unplanned Returns to Hospital within 30 Days of Discharge from Medical Wards" – *Dr. Romina Pace, McGill University*

"The Evolution of the Body Mass Index Distribution in Populations" – *Dr. Fahad Razak, University of Toronto*

"Vaccination Rates of Halifax's Homeless: Are There Barriers to Vaccine Delivery and Uptake?" – *Dr. Colin Van Zoost, Dalhousie University*

Research Posters, First Session

"Managing Complex Patients According to Guidelines without Lifting a Finger" – *Dr. Patrick Darragh, University of Toronto*

"Higher Risk of Severe Post-operative Cardio-pulmonary Complications in Patients with Severe Obstructive Sleep Apnea" – *Dr. Vincent Déry, Université de Sherbrooke*

"A Failure to Communicate? An Investigation of Medicine Handover" – *Dr. Caroline Hart, University of Saskatchewan*

"Obesity and Outcomes in Patients Hospitalized with Pneumonia" – *Dr. Sharry Kahlon, University of Alberta*

"Barriers to the Use of Nicotine Replacement Therapy for Smoking Cessation in Young Smokers" – *Dr. Andrea Kermack, McGill University*

"Baseline Knowledge and Performance of Ankle-Brachial Index (ABI) among Internal Medicine (IM) Residents at the University of X (U of X)" – *Dr. Upul Madampage, University of Saskatchewan*

"The Effect of Structured Peer Review and Feedback on Residents' Ability to Write Effective Consultation Letters" – *Dr. Ning-Zi Sun, McGill University*

"Comparison of a Three-Point versus a Two-Point Binary Checklist for Assessment of Procedural Skills" – *Dr. Alison Walzak, University of Calgary*

"Enhancing Clinical Clerks' Participation and Learning at Internal Medicine Morning Report: Results of an Online Survey" – *Dr. Tina Zhu, University of Toronto*

Clinical Posters, First Session

"Poorly Differentiated Adenocarcinoma in a Male Presenting with Ascites" – *Dr. Angela Assal, University of Ottawa*

"An Unusual Case of Diabetic Ketoacidosis Precipitated by Cannabinoid Hyperemesis Syndrome" – *Dr. Erin Carter, University of Calgary*

"Peripheral T-Cell Lymphoma, Not Otherwise Specified (NOS), with Associated T-Cell Mediated Vasculitis" – *Dr. Derek Chew, University of Calgary*

"Mitochondrial Disease and Renal Transplant" – *Dr. Mohan Cooray, McMaster University*

"Diffuse Melanosis in a Patient with Metastatic Melanoma" – *Dr. Janeve Everett, McGill University*

"Cotton Fever – A Street Diagnosis Brought to Light in the ER" – *Dr. Sonja Gill, State University of New York*

"Are You Still Feverish?" – *Dr. Isabelle Guité, Université de Sherbrooke*

"Diffuse Melanosis Cutis Secondary to Metastatic Malignant Melanoma" – *Dr. Lucy Lu, McMaster University*

"Renal Cell Carcinoma Masquerading as Polymyalgia Rheumatica" – *Dr. Kelly McGowan, University of Toronto*

"A Taste of Protein" – *Mlle Claudia Rochefort, McGill University*

"Palpation and Auscultation to Diagnose Large Vessel Giant Cell Arteritis" – Dr. Pamela Tsao, University of Toronto

"Sweet's Syndrome: An Unsavoury Effect of Filgrastim" – *Ms. Jane Turner, Western University*

Ted Giles Clinical Vignettes 2012
Oral Presentations

"Dyspnea in a Patient with Amyopathic Dermatomyositis" – *Dr. Janeve Everett, McGill University*

"When the Liver Fails to Deliver" – *Dr. Runye Gan, McGill University*

"A Classic Presentation of a Rare Condition" – *Dr. Cameron Gilbert, University of Toronto*

"A Case of Addison's Disease with Initially Normal Cortisol: When Labs Lag Behind Symptoms" – *Dr. Laura Hinz, University of Calgary*

"Intraoperative Myocardial Infarction: A Case of Kounis Syndrome Provoked by Latex Allergy" – *Dr. Veronica Marcoux, University of Saskatchewan*

"An Unusual Case of Anemia" – *Dr. Varinder Randhawa, University of Toronto*

"Fungal Masquerade – A Cover-Up for a Case of Pyoderma Gangrenosum" – *Dr. Benjamin Shieh, Queen's University*

"The Numbing Truth about Salt Replacements" – *Dr. Shankar Sivananthan, University of Toronto*

"Blood Really Is Thicker Than Water …" – *Dr. Jenna Tessolini, University of Toronto*

"It All Adds Up: A Case of Severe Hypercalcemia" – *Dr. Ben Wilson, University of Calgary*

Research Posters, Second Session

"Incidence Study of Seronegative Spondyloarthropathy in a Rural Region of Canada" – *Dr Richard Audet, Laval and McGill Universities*

"Treating Dyslipidemia in Patients at High Risk of a Cardiovascular Event in a Rural Canadian Population" – *Dr Richard Audet, Laval and McGill Universities*

"Atrioventricular Nodal Re-entry Tachycardia in Identical Twins: A Case Report and Literature Review" – *Dr. Walid Barake, Queen's University*

"Maternal Obesity and the Risk of Preeclampsia in IVF Pregnancies: A Retrospective Cohort Study" – *Dr. Natalie Dayan, McGill University*

"Cardiovascular Adverse Events with Adjuvant Endocrine Therapy for Early Breast Cancer. Tamoxifen vs. Aromatase Inhibitors: Systematic Review – Evidence from RCTs" – *Dr. Don Thiwanka Dilshan, Queen's University*

"The Implementation and Evaluation of an Innovative Mentorship Programme for Internal Medicine Residents" – *Dr. Rahim Kachra, University of Calgary*

"Diabetic Foot Infections and Antibiotic Resistance: Insights from Cameroon, Sub-Saharan Africa" – *Mr. Brice Nouthe, McGill University*

"Global Health Education: Needs Assessment amongst Postgraduate Internal Medicine Residents at a Canadian Academic Institution" – *Dr. Ameen Patel, McMaster University*

"Preoperative Analgesic Care for Hip Fractures: A Retrospective Chart Review" – *Dr. Jeffrey Segal, McGill University*

"Timeliness of Antibiotic Administration and Outcome of Bacterial Meningitis in Adults Admitted to a Teaching Hospital" – *Dr. Oleg Veselskiy, University of Saskatchewan*

Clinical Posters, Second Session

"Reevaluating Vasopressin in the Septic Patient – A Case of Acquired Transient SIADH with Initiation of Therapeutic Vasopressin" – *Dr. Ifrah Abdirahman, University of Ottawa*

"Asymptomatic Persistent Eosinophilia" – *Dr. Wael Alqarawi, University of Toronto*

"Fever in the Returned Traveller – An Interesting Case of Feeling Run Down Even When the Runs Are Gone" – *Ms. Angela Chan, McMaster University*

"An UncharacterisTIC Cause of Abdominal Pain" – *Dr. Mohan Cooray, McMaster University*

"Chronic Diarrhea and Immunosuppression: A Common Pathogen Behaving in an Uncommon Way" – *Dr. Mohan Cooray, McMaster University*

"An Unexpected Cause of Spinal Cord Compression" – *Dr. Cameron Gilbert, University of Toronto*

"An Uncommonly Sweet (Disease) Presentation of Ulcers and Rash" – *Dr. Meghan Ho, University of British Columbia*

"Congestive Heart Failure Due to Gastrointestinal Stromal Tumor: An Uncommon Presentation of a Rare Disease" – *Dr. Sheila Klassen, McMaster University*

"Leukemia Cutis in Myelomonocytic Leukemia" – *Dr. Mita Manna, University of Saskatchewan*

"To Biopsy or Not to Biopsy" – *Dr. Fahad Razak, University of Toronto*

"Insufficiency Fractures during Pregnancy as First Presentation of Hypercortisolism" – *Dr. Alyssa Shariff, University of Saskatchewan*

Please visit http://www.csimonline.com/ to access the full abstracts.

In their article "End-of-Life Decisions: A Case Report and Clinician's Guide Focusing on Situations of Disagreement between the Medical Team and Substitute Decision Maker," Bollegala et al.[1] focus upon managing disagreements about end-of-life care. Unfortunately, the case provides more questions than answers and fails to give any clear guidance to clinicians to prevent such a tragic outcome from recurring.

They describe an elderly patient suffering from advanced dementia who was previously admitted with aspiration pneumonia and was then taken from hospital by family members against medical advice (AMA). Were family members aware that the patient was at or nearing the end of his life and that the dementia was reaching a terminal phase? Was time taken to establish the prognosis in an emotionally supportive way? What was the nature of the disagreement that resulted in the patient being taken away AMA?

After readmission, swallowing assessment showed the patient to be at high risk of aspiration but the family refused (chose?) not to have a feeding tube placed. Why was a feeding tube offered? What were the established goals, if any? Were the clinicians aware that feeding tubes in elderly patients with advanced dementia are of no proven benefit?[2] Were conservative measures taken to minimize aspiration risk, such as head positioning and thickened fluids?

We are told that despite the medical team's assessment of a poor prognosis, family members insisted upon full treatment including CPR and ICU admission. What is a poor prognosis? Is it the same as dying? Were the families members told and helped to understand that the patient was dying due to profound and untreatable dementia? Was psychological and emotional support offered to help them come to terms with the impending death?

Fundamentally, the authors described repeated and strenuous efforts to persuade family members to agree with the medical team. Irrespective of the strength of either side's arguments or ethics, this process establishes that decisional authority lies with the next of kin. A recent editorial in a flagship medical journal describes an alternative to such a conciliatory negotiation process.[3]

In Halifax, a PATH (palliative and therapeutic harmonization) clinic has been established to ensure frail and often terminally ill patients receive care congruent with their needs (see http://www.cdha.nshealth.ca/geriatric-medicine/palliative-therapeutic-harmonization-clinic/principles-path-clinic). This type of proactive care process offers an important model for the future.

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3. Blinderman CD, Krakauer EL, Solomon MZ. Time to revise the approach to determining cardiopulmonary resuscitation status. JAMA 2012;307(9):917–8. doi: 10.1001/jama.2012.236.

BRILINTA®
ticagrelor tablets

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Platelet Aggregation Inhibitor

INDICATIONS AND CLINICAL USE: BRILINTA (ticagrelor), co-administered with acetylsalicylic acid (ASA), is indicated for the secondary prevention of atherothrombotic events in patients with Acute Coronary Syndromes (ACS) (unstable angina [UA], non–ST Elevation Myocardial Infarction [NSTEMI] or ST Elevation Myocardial Infarction [STEMI]) who are to be managed medically and those who are to be managed with percutaneous coronary intervention (PCI) (with or without stent) and/or coronary artery bypass graft (CABG).

Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of BRILINTA compared to clopidogrel, BRILINTA is recommended to be co-administered with low maintenance dose ASA (75-150 mg daily).

Pediatrics (<18 years of age): The safety and efficacy of BRILINTA in pediatric patients below the age of 18 have not been established. Therefore, BRILINTA is not recommended in this population.

CONTRAINDICATIONS: BRILINTA (ticagrelor) is contraindicated in:

- Patients who are hypersensitive to this medication or to any ingredient in the formulation
- Patients who have active pathological bleeding such as peptic ulcer or intracranial hemorrhage
- Patients with a history of intracranial hemorrhage
- Patients with moderate to severe hepatic impairment
- Patients who are also taking strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir), as it may lead to a substantial increase in exposure to ticagrelor

SPECIAL POPULATIONS:

Pregnant Women: The safety of BRILINTA during pregnancy has not been established, as no clinical study has been conducted in pregnant women and limited clinical data on exposure to BRILINTA during pregnancy are available. Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy.

Nursing Women: It is not known whether this drug is excreted in human milk, as no clinical study has been conducted in lactating women. Studies in rats have shown that ticagrelor and its active metabolites are excreted in milk. Therefore, the use of BRILINTA during breastfeeding is not recommended.

Geriatrics (≥65 years of age): In PLATO, 43.1% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Pediatrics (<18 years of age): The safety and efficacy of BRILINTA in pediatric patients below the age of 18 have not been established. Therefore, BRILINTA is not recommended in this population.

Hepatic Impairment: Use of BRILINTA is contraindicated in patients with moderate or severe hepatic impairment.

Renal Impairment: No dose adjustment is necessary for patients with renal impairment. No clinical study has been conducted in patients on renal dialysis. Ticagrelor is not thought to be dialyzable. Appropriate caution should be used in patients requiring renal replacement therapy. Creatinine levels may increase during treatment with BRILINTA. The mechanism has not been identified. Renal function should be monitored in the course of patient management.

Uric Acid Increase: In PLATO, patients on BRILINTA had a higher risk of hyperuricemia than those receiving clopidogrel. Caution should be exercised when administering BRILINTA to patients with history of hyperuricemia or gouty arthritis. As a precautionary measure, the use of BRILINTA in patients with uric acid nephropathy is discouraged.

Safety Information

WARNINGS AND PRECAUTIONS:

General

Bleeding Risk: As with other antiplatelet agents, the use of BRILINTA (ticagrelor) in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events.

If clinically indicated, BRILINTA should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g., due to recent trauma, recent surgery, active or recent gastrointestinal bleeding, or moderate hepatic impairment). The use of BRILINTA is contraindicated in patients with active pathological bleeding, in those with history of intracranial hemorrhage, and moderate to severe hepatic impairment.
- Patients requiring oral anticoagulants (e.g., warfarin) and/or fibrinolytics agents (within 24 hours of BRILINTA dosing). Such agents confer an independent bleeding risk as they function in a distinct and complementary mechanism of hemostasis compared to BRILINTA. The combination of BRILINTA with either of these classes of drugs has not been studied.
  - **Warfarin Therapy:** Due to an increased propensity to bleed, caution is advised in patients taking warfarin during BRILINTA therapy. A specific drug-drug interaction study with warfarin has not been performed.
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding, e.g., non-steroidal anti-inflammatory drugs (NSAIDs).

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions; circulating BRILINTA may inhibit transfused platelets. Since co-administration of BRILINTA with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa may augment hemostasis. BRILINTA may be resumed after the cause of bleeding has been identified and controlled.

Maintenance Dose Acetylsalicylic acid (ASA): Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of BRILINTA compared to clopidogrel, co-administration of BRILINTA and high maintenance dose ASA (>150 mg daily) is not recommended.

Cytochrome P450 3A4 Strong Inhibitors: Co-administration of BRILINTA with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir) is contraindicated as co-administration may lead to a substantial increase in exposure to ticagrelor.

Peri-Operative Considerations

Surgery: If a patient requires surgery, clinicians should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of BRILINTA treatment should occur.

To minimize the risk of bleeding, if a patient is to undergo elective surgery and antiplatelet effect is not desired, BRILINTA should be discontinued 5 days prior to surgery.

Respiratory

Dyspnea: In PLATO, approximately 13.8% of patients randomized to BRILINTA, versus 7.8% for clopidogrel, reported dyspnea, including dyspnea at rest, exertional dyspnea, paroxysmal nocturnal dyspnea and nocturnal dyspnea. The dyspnea is usually mild to moderate in intensity and often resolves during continued BRILINTA treatment. The mechanism has not yet been elucidated. If a patient reports new, prolonged or worsened dyspnea this should be investigated fully and if not tolerated, treatment with BRILINTA should be stopped.

ADVERSE REACTION SERIOUSNESS AND INCIDENCE:

Adverse Drug Reaction Overview: The commonly reported adverse events in patients treated with BRILINTA (ticagrelor) were dyspnea, headache and epistaxis and these events occurred at higher rates than in the clopidogrel treatment group (see Table 1).

Table 1: Summary of Adverse Events (Regardless of Causality) Reported for ≥1% of Patients in Either Group (PLATO)

Adverse Event (System Organ Class)	BRILINTA (%) N=9235	Clopidogrel (%) N=9186
Blood and Lymphatic System Disorders		
Anemia	1.9	1.7
Cardiac Disorders		
Atrial fibrillation	4.2	4.6
Bradycardia[a]	2.9	2.9
Cardiac failure	2.3	2.6
Ventricular tachycardia	2.0	2.1
Palpitations	1.2	1.1
Angina pectoris	1.2	1.1
Sinus bradycardia	1.1	0.8
Ventricular extrasystoles	1.1	1.1
Ventricular fibrillation	0.8	1.0
Ear and Labyrinth Disorders		
Vertigo[b]	1.5	1.3
Gastrointestinal Disorders		
Nausea[b]	4.3	3.8
Diarrhea[b]	3.7	3.3
Vomiting[b]	2.5	2.3
Constipation[b]	2.2	2.6
Dyspepsia[b]	2.0	1.8
Abdominal pain upper	1.9	2.0
Abdominal pain[b]	1.5	1.2
General Disorders and Administration Site Conditions		
Non-cardiac chest pain	3.7	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5
Pyrexia	2.9	2.8
Edema peripheral	2.3	2.5
Asthenia	2.0	2.1
Hemorrhages or bleeding		
Epistaxis[b]	6.0	3.4
Contusion	3.9	2.0
Hematoma	2.2	1.3
Post-procedural hemorrhage[b]	2.1	2.0
Vessel puncture site hematoma	1.7	1.1
Ecchymosis	1.5	0.6
Infections and Infestations		
Urinary tract infection	2.0	1.8
Hematuria	1.9	1.6
Nasopharyngitis	1.8	1.6
Pneumonia	1.4	1.9
Bronchitis	1.3	1.4
Metabolism and Nutrition Disorders		
Diabetes mellitus	1.2	1.1
Dyslipidemia	1.0	1.0
Hypercholesterolemia	1.0	0.9
Hypokalemia	1.6	1.5
Musculoskeletal and Connective Tissue Disorders		
Back pain	3.6	3.3
Pain in extremity	2.1	2.3
Musculoskeletal chest pain	1.5	1.4
Musculoskeletal pain	1.5	1.5
Arthralgia	1.5	1.4
Myalgia	1.4	1.6
Nervous System Disorders		
Headache[b]	6.5	5.8
Dizziness[b]	4.5	3.9
Syncope	1.1	0.8
Psychiatric Disorders		
Anxiety	2.2	1.9
Insomnia	1.7	2.0
Depression	1.1	1.1
Renal and Urinary Disorders		
Renal failure	1.0	0.7
Respiratory Disorders		
Dyspnea[a,b]	12.0	6.5
Cough	4.9	4.6
Dyspnea exertional	1.9	1.4
Skin and Subcutaneous Tissue Disorders		
Rash[b]	1.8	1.7
Pruritus[b]	1.0	1.0
Vascular Disorders		
Hypertension	3.8	4.0
Hypotension	3.2	3.3

a Several MedDRA PT combined.
b These events have also been reported as Adverse Drug Reactions (possibly or probably related to BRILINTA).

DRUG INTERACTIONS: Cytochrome P450 (CYP) 3A4/5 are the major enzymes responsible for the metabolism of BRILINTA (ticagrelor) and the formation of the active metabolite. Clinical pharmacology and *in vitro* data show that there is a complex interaction between ticagrelor and CYP3A4/5. Indeed, depending on the substrate, ticagrelor and its active metabolite are shown to weakly inhibit or weakly activate CYP3A4/5 (see DETAILED PHARMACOLOGY). Therefore, co-administration of BRILINTA and CYP3A4/5 substrates with narrow therapeutic indices is not recommended. CYP enzymes 1A2, 2C19 and 2E1 do not contribute meaningfully *in vitro* to ticagrelor metabolism. BRILINTA is also a p-glycoprotein (P-gp) substrate and a weak inhibitor of P-gp.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
Fax toll-free to 1-866-678-6789, or
Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage-paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at www.healthcanada.gc.ca/medeffect.

Administration

Recommended Dose

BRILINTA therapy should be initiated with a single 180 mg oral loading dose (two 90 mg tablets) and then continued at 90 mg twice daily. Patients taking BRILINTA should also take acetylsalicylic acid (ASA) daily, unless specifically contraindicated. Following an initial loading dose of ASA, BRILINTA should be used with a daily maintenance dose of ASA of 75-150 mg.

BRILINTA can be taken orally with or without food. In a study of healthy subjects, ingestion of a high-fat meal had no effect on ticagrelor C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max}. These changes are considered of minimal clinical significance. BRILINTA was administered without regard to food in PLATO.

Grapefruit juice interaction: A drug-drug interaction study with grapefruit juice has not been performed. Based on the pharmacokinetic data for ticagrelor, grapefruit juice is expected to increase ticagrelor exposure to a clinically insignificant extent. Therefore, BRILINTA can be taken with grapefruit juice.

Missed Dose

Lapses in therapy should be avoided. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

SUPPLEMENTAL PRODUCT INFORMATION

WARNINGS AND PRECAUTIONS:

Discontinuations: Patients who require discontinuation of BRILINTA are at increased risk for cardiac events. Premature discontinuation of treatment should be avoided. If BRILINTA must be temporarily stopped due to an adverse event, it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution.

Cardiovascular

Patients at Risk for Bradycardic Events: Due to observations of mostly asymptomatic ventricular pauses in an earlier clinical study, the Phase III study (PLATO) excluded patients with an increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope and not protected with a pacemaker). Therefore, due to the limited clinical experience, BRILINTA should be used with caution in these patients.

In addition, caution should be exercised when administering BRILINTA concomitantly with drugs known to induce bradycardia. However, no evidence of clinically significant adverse interactions was observed in the PLATO trial during concomitant administration with one or more drugs known to induce bradycardia: in PLATO, 96% of patients took beta-blockers, 33% took diltiazem or verapamil (calcium channel blockers) and 4% took digoxin.

Neurologic

Effects on Ability to Drive and Use Machines: No studies on the effects of BRILINTA on the ability to drive and use machines have been performed. BRILINTA has no or negligible influence on the ability to drive and use machines. During treatment for Acute Coronary Syndromes, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

Peri-Operative Considerations

In PLATO patients undergoing CABG, BRILINTA had a similar rate of major bleeds compared to clopidogrel at all days after stopping therapy except Day 1 where BRILINTA had a higher rate of major bleeding.

Because of the reversible binding of BRILINTA, restoration of platelet aggregation occurs faster with BRILINTA compared to clopidogrel.

In the OFFSET study, mean Inhibition of Platelet Aggregation (IPA) for ticagrelor at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The more rapid offset of effect may predict a reduced risk of bleeding complications, e.g., in settings where antiplatelet therapy must be temporarily discontinued due to surgery or trauma.

Adverse Drug Reaction Overview

In PLATO, a total of 6762 patients with Acute Coronary Syndromes (UA, NSTEMI and STEMI) were exposed to BRILINTA (180 mg loading dose followed by a 90 mg twice daily maintenance dose) for at least 6 months and up to 12 months for 3138 of them.

Serious adverse events were reported in a similar frequency between BRILINTA (20.2%) and clopidogrel (20.3%) treated patients. The most frequent serious adverse events observed were cardiac failure (1.1% vs. 1.0%), non-cardiac chest pain (0.9% vs. 0.9%) and dyspnea (0.7% vs. 0.4%).

The rate of study drug discontinuation because of adverse events was 7.4% for BRILINTA and 5.4% for clopidogrel. Dyspnea was the most common adverse event leading to study drug discontinuation for BRILINTA (0.9% for BRILINTA and 0.1% for clopidogrel).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Bleeding Events: The primary safety endpoint in the PLATO study was the composite endpoint of 'Total Major' bleeding, which consisted of the components of 'Major Fatal/Life-threatening' and 'Major Other'. Table 2 shows the 12-month rates of patients experiencing bleeding events in the PLATO study (PLATO-defined).

Table 2: Analysis of Overall Bleeding Events – PLATO-defined

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186	*p*-value*
Primary Safety Endpoint			
Total Major	11.6	11.2	0.4336
Secondary Safety Endpoints			
Major Fatal/Life-threatening	5.8	5.8	0.6988
Combined Total Major + Minor	16.1	14.6	0.0084
Non-procedural Major	3.1	2.3	0.0058
Non-procedural Major + Minor	5.9	4.3	<0.0001
Non-CABG Total Major	4.5	3.8	0.0264
Non-CABG Major Fatal/Life-threatening	2.1	1.9	0.2516

*Nominal *p*-value not corrected for multiple testing.
Major Fatal/Life-threatening: Clinically apparent with >50 g/L decrease in hemoglobin or ≥4 red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolemic shock or severe hypotension requiring pressors or surgery.
Major Other: Clinically apparent with 30-50 g/L decrease in hemoglobin or 2-3 red cell units transfused; or significantly disabling.
Minor: Requires medical intervention to stop or treat bleeding.

There were few fatal bleeding events in the study, 20 (0.2%) for BRILINTA and 23 (0.3%) for clopidogrel. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on BRILINTA than on clopidogrel.

Location of 'Total Major + Minor' Bleeding (BRILINTA vs. clopidogrel): Intracranial 0.3% vs. 0.2%, pericardial 0.1% vs. 0.1%, retroperitoneal 0.03% vs. 0.03%, intraocular 0.02% vs. 0.04% and intra-articular 0.02% vs. 0.01%. Other common locations were in rank order of event frequency: gastrointestinal 1.8% vs. 1.5%, epistaxis 1.3% vs. 0.7%, urinary 0.5% vs. 0.4%, subcutaneous/dermal 0.5% vs. 0.4% and hemoptysis 0.1% vs. 0.08%.

Non-procedural Fatal Bleeding: There was no difference with BRILINTA compared to clopidogrel for overall non-procedural fatal bleeding. There were numerically more 'Major Fatal/Life-threatening' intracranial non-procedural bleeding events with BRILINTA (n=27 events, 0.3%) than with clopidogrel (n=14 events, 0.2%). Of the intracranial non-procedural bleeding events, 11 bleeding events with BRILINTA and 1 with clopidogrel were fatal. 'Major Fatal/Life-threatening' gastrointestinal bleeding was the same with BRILINTA and clopidogrel, with numerically more fatal events for clopidogrel (5) than for BRILINTA (none).

Bleeding in Subgroups Patient Population: Baseline characteristics including age, gender, weight, race, geographic region, medical history, concurrent conditions and concomitant therapy were assessed to explore any increase in risk of bleeding with BRILINTA. No particular risk group was identified for any subset of bleeding.

Table 3 shows the overall rates of TIMI-defined bleeding events.

Table 3: Analysis of Overall Bleeding Events – TIMI-defined

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186	*p*-value
Major	7.9	7.7	0.5669
Major + Minor	11.4	10.9	0.3272
Non-CABG Major	2.8	2.2	0.0246
Non-CABG Major + Minor	4.5	3.6	0.0093

TIMI Major: Clinically apparent with >50 g/L decrease in hemoglobin or intracranial hemorrhage.
TIMI Minor: Clinically apparent with 30 to ≤50 g/L decrease in hemoglobin.

Additional clinical Adverse Drug Reactions that were reported as possibly or probably related to BRILINTA are listed below by body system:

Common (≥1% to <10%)
- *Skin and subcutaneous tissue disorders:* subcutaneous or dermal bleeding
- *Gastrointestinal disorders:* gastrointestinal hemorrhages
- *Renal and urinary disorders:* urinary tract bleeding

Uncommon (≥0.1% to <1%)
- *Nervous system disorders:* intracranial hemorrhage (may be fatal or life threatening), confusion, paraesthesia
- *Gastrointestinal disorders:* gastritis, retroperitoneal hemorrhage
- *Eye disorders:* eye hemorrhage (intraocular, conjunctival, retinal)
- *Respiratory, thoracic and mediastinal disorders:* hemoptysis

Rare (≥0.01% to <0.1%)
- *Musculoskeletal connective tissue and bone:* hemarthrosis

DRUG INTERACTIONS:

Drug-Drug Interactions

Effects of Other Drugs on BRILINTA

Ketoconazole (Strong CYP3A4 Inhibitors): Co-administration of ketoconazole with ticagrelor increased the ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of ticagrelor's active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir and atazanavir) would be expected to have similar effects and are contraindicated with BRILINTA.

Diltiazem (Moderate CYP3A4 Inhibitors): Co-administration of diltiazem with ticagrelor increased the ticagrelor C_{max} by 69% and AUC by 174% and decreased its active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, erythromycin, fluconazole and verapamil) would be expected to have similar effects. These exposure changes are not considered clinically significant, and therefore can as well be co-administered with BRILINTA.

Rifampin and Other CYP3A4 Inducers: Co-administration of rifampin with ticagrelor decreased the ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of its active metabolite was unchanged and the AUC was decreased by 46%. Other CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to ticagrelor as well and may result in reduced efficacy of BRILINTA.

Others: Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin and acetylsalicylic acid (ASA) did not have any effect on ticagrelor or its active metabolite plasma levels. Co-administration of ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. Co-administration of ticagrelor and enoxaparin had no effect on enoxaparin based on factor Xa assay.

Effects of BRILINTA on Other Drugs

Simvastatin: Co-administration of ticagrelor with simvastatin increased the simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2- to 3-fold. Consideration of the clinical significance should be given to the magnitude and range of changes on the exposure to patients requiring greater than 40 mg of simvastatin. There was no effect of simvastatin on ticagrelor plasma levels. BRILINTA may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins.

Atorvastatin: Co-administration of atorvastatin and ticagrelor increased the atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

Tolbutamide: Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug, which demonstrates ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the metabolism of other drugs metabolized via CYP2C9.

Warfarin: A drug-drug interaction study with warfarin has not been performed. As with other oral antiplatelet therapy, there is a potential for increased risk of bleeding, therefore, warfarin and BRILINTA should be co-administered with caution.

Oral Contraceptives: Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased the ethinyl estradiol exposure approximately 20% but did not alter the PK of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with BRILINTA.

Digoxin (P-gp Substrate): Concomitant administration of ticagrelor increased the digoxin C_{max} by 75% and AUC by 28%. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin concomitantly with BRILINTA.

Other Concomitant Therapy: In clinical studies, BRILINTA was commonly administered with ASA, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions.

DOSAGE AND ADMINISTRATION:

General

The PLATO trial data suggest the efficacy of BRILINTA (ticagrelor) relative to clopidogrel is associated with ASA dose during maintenance therapy. Patients receiving a low maintenance dose of ASA benefit more than those receiving a high maintenance dose of ASA. Because the data from patients receiving high maintenance dose ASA (>300 mg daily) do not provide conclusive evidence of the efficacy of BRILINTA compared to clopidogrel, high maintenance dose ASA (>150 mg daily) is not recommended for maintenance dual antiplatelet therapy with BRILINTA. There is no conclusive evidence regarding the underlying biological mechanism. Based on analysis of the available clinical data, it is recommended that BRILINTA be used with a daily low maintenance dose of ASA (75-150 mg).

Furthermore, no safety and efficacy data is available on the use of BRILINTA beyond one year treatment duration.

Recommended Dose and Dosage Adjustment

Switching from clopidogrel to BRILINTA: Patients can be switched from clopidogrel to BRILINTA without interruption of antiplatelet effect. This results in an absolute inhibition of platelet aggregation (IPA) increase of 26.4%. Conversely, switching from BRILINTA to clopidogrel results in an absolute IPA decrease of 24.5%. Clinicians who desire to switch patients from clopidogrel to BRILINTA should administer the first 90 mg dose of BRILINTA 24 hours following the last dose of clopidogrel.

Dosing Considerations in Special Populations

Geriatrics (≥65 years of age): No dosage adjustment is required in elderly (≥65 years) patients.

Patients with Renal Insufficiency: No dosage adjustment is required in patients with renal impairment. No clinical study has been conducted in patients on renal dialysis. Ticagrelor is not thought to be dialyzable. Appropriate caution should be used in patients requiring renal replacement therapy.

Patients with Hepatic Insufficiency: No dosage adjustment is required in patients with mild hepatic impairment. BRILINTA has not been studied in patients with moderate or severe hepatic impairment.

OVERDOSAGE:

For management of suspected drug overdose, contact your regional Poison Control Centre.

Treatment

There is currently no known antidote to reverse the effects of BRILINTA (ticagrelor), and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. The expected effect of excessive BRILINTA dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs, appropriate supportive measures should be taken.

ACTION AND CLINICAL PHARMACOLOGY:

Pharmacodynamics

Inhibition of platelet aggregation (IPA) mediated by ticagrelor increases with increasing plasma concentrations of ticagrelor and its active metabolite (AR-C124910XX), until almost complete inhibition is attained. The inhibition of platelet aggregation gradually decreases with declining plasma ticagrelor and active metabolite concentrations, as the IPA mediated by ticagrelor is reversible. Since ticagrelor reversibly binds to the $P2Y_{12}$ receptor, the recovery of platelet function is expected to be dependent on the plasma concentrations of ticagrelor and the active metabolite and not on the replacement of irreversibly inhibited platelets as with thienopyridine antiplatelet agents.

The IPA of ticagrelor is generally independent of factors such as race, hepatic or renal disease or co-administered ASA, heparin and enoxaparin.

Pharmacokinetics

Ticagrelor demonstrates linear pharmacokinetics. Exposure to ticagrelor and its active metabolite are approximately dose proportional.

Date of Preparation: May 26, 2011

The Prescribing Summary provides the most current information at the time of printing. For access to the most up-to-date information, view the full Product Monograph (prepared for health professionals) by visiting www.astrazeneca.ca or by contacting AstraZeneca Canada Inc.

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Mississauga, Ontario L4Y 1M4
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Pr Samsca® (tolvaptan)

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Vasopressin V_2-receptor Antagonist

INDICATIONS AND CLINICAL USE

PRSAMSCA® (tolvaptan) is indicated for the treatment of clinically important, non-hypovolemic hyponatremia, e.g., serum sodium <130 mEq/L, or symptomatic hyponatremia.

SAMSCA should be limited to use by physicians experienced in the management of clinically important hyponatremia.

SAMSCA has not been studied in patients with serious neurological symptoms requiring urgent correction of serum sodium. Patients requiring urgent intervention to raise serum sodium to treat serious neurological symptoms associated with hyponatremia should not be treated with SAMSCA.

It has not been established that raising serum sodium with SAMSCA provides symptomatic benefit to patients or improvement in clinical outcomes.

CONTRAINDICATIONS

SAMSCA (tolvaptan) is contraindicated in the following conditions: hypovolemic hyponatremia, urgent need to raise serum sodium acutely, inability of the patient to sense or appropriately respond to thirst, concomitant use of strong CYP 3A inhibitors, e.g., ketoconazole, clarithromycin, ritonavir, saquinivir, nefazodone, anuric patients, in patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING in the Product Monograph.

SPECIAL POPULATIONS (see full listing in Supplemental Product Information section)

Pregnant Women: There are no adequate and well controlled trials of SAMSCA use in pregnant women. In animal trials, cleft palate, brachymelia, microphthalmia, skeletal malformations, decreased fetal weight, delayed fetal ossification, and embryo-fetal death occurred. SAMSCA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: It is not known whether SAMSCA is secreted into human milk. The presence of tolvaptan has been observed in the milk of lactating rats. Because many drugs are secreted into human milk and because of the potential for serious adverse reactions in nursing infants from SAMSCA, a decision should be made whether to discontinue nursing or the administration of tolvaptan, taking into consideration the importance of SAMSCA to the mother.

Pediatrics (<18 years of age): Safety and effectiveness of SAMSCA in pediatric patients have not been established.

Geriatrics (>65 years of age): Of the total number of hyponatremic patients treated with SAMSCA in clinical trials, 42% were 65 and over, while 19% were 75 and over. No overall differences in safety or effectiveness were observed between older patients and younger ones. Other reported clinical experience has also not identified differences in responses between the elderly and younger patients, however, greater sensitivity of some older individuals cannot be ruled out. Increasing age has no effect on tolvaptan plasma concentrations.

Hepatic Impairment: Moderate and severe hepatic impairment do not affect exposure to tolvaptan to a clinically relevant extent. No dose adjustment of tolvaptan is necessary.

Renal Impairment: Exposure and response to tolvaptan are similar in patients with a creatinine clearance 10-79 mL/min and in patients without renal impairment. No dose adjustment is necessary. Exposure and response to tolvaptan in patients with a creatinine clearance <10 mL/min or in patients on chronic dialysis have not been studied. Note that no benefit can be expected in patients who are anuric.

Heart Failure: The exposure to tolvaptan in patients with heart failure is not clinically relevantly increased. No dose adjustment is necessary.

Safety Information

WARNINGS AND PRECAUTIONS

SAMSCA (tolvaptan) should be initiated, or re-initiated, only in hospital where serum sodium can be monitored closely by physicians experienced in the management of clinically important hyponatremia. Too rapid correction of hyponatremia, e.g., >12 mEq/L over 24 hours, can cause osmotic demyelination which may result in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. In susceptible patients, including those with severe malnutrition, alcoholism, or advanced liver disease, slower rates of correction may be advisable.

General: Patients with hyponatremia whose serum sodium concentration is increased too rapidly (e.g., >8 mEq/L/first 8 hours or >12 mEq/L/24 hours) may be at risk for serious neurologic sequelae. In controlled clinical trials, this rapid rate of sodium correction had been observed in approximately 3% of patients treated with tolvaptan (n=223) and 0% of placebo-treated patients (n=220), in titrated doses of SAMSCA between 15 mg/day and 60 mg/day. Patients treated with tolvaptan should be monitored to assess serum sodium concentrations and neurologic status, especially during initiation and after titration. Patients with syndrome of inappropriate anti-diuretic hormone (SIADH) or very low baseline serum sodium concentrations may be at greater risk for too rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium, discontinue or interrupt treatment with SAMSCA, and consider administration of hypotonic fluid. Fluid restriction during the first 24 hours of therapy with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.

Osmotic demyelination syndrome (ODS) is a condition associated with too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours). Osmotic demyelination may result in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. None of the patients in the controlled clinical trials with tolvaptan exhibited evidence of osmotic demyelination syndrome or related neurological sequelae, but such complications have been reported following too rapid correction of serum sodium. There is no experience with concomitant use of SAMSCA and hypertonic saline. Concomitant use with hypertonic saline is not recommended.

Dehydration: SAMSCA therapy induces copious aquaresis, which is normally partially offset by fluid intake. Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted. In multiple-dose, placebo-controlled trials in which 607 hyponatremic patients were treated with tolvaptan, the incidence of dehydration was 3.3% for tolvaptan and 1.5% for placebo-treated patients. In patients receiving SAMSCA who develop medically significant signs or symptoms of hypovolemia, interrupt or discontinue SAMSCA therapy and provide supportive care with careful management of vital signs, fluid balance and electrolytes. Fluid restriction during therapy with SAMSCA may increase the risk of dehydration and hypovolemia. Patients receiving SAMSCA should continue ingestion of fluid in response to thirst.

Gastrointestinal: While the overall risk of hemorrhage was similar to placebo in the total population studied to date, in patients with cirrhosis studied in hyponatremia trials, gastrointestinal bleeding was reported in 6 of 63 (10%) tolvaptan-treated patients and 1 of 57 (2%) placebo-treated patients.

Laboratory Findings: Treatment with tolvaptan may be associated with a modest increase in serum potassium.

ADVERSE REACTIONS (see full listing in Supplemental Product Information section)

Adverse Drug Reaction Overview: Overall, over 4,000 patients have been treated with oral doses of SAMSCA (tolvaptan) in placebo-controlled or open-label clinical trials. Approximately 650 of these patients had hyponatremia, and approximately 219 of these hyponatremic patients were treated with tolvaptan for 6 months or more. About 223 patients with hyponatremia received tolvaptan in pivotal trials dedicated to evaluate its effects in the treatment of hyponatremia. Other patients with hyponatremia were evaluated in chronic heart failure trials. The most common adverse reactions, at an incidence >5% more than placebo, as seen in two 30-day, double-blind, placebo-controlled hyponatremia trials in which tolvaptan was administered in titrated doses of 15 mg to 60 mg once daily, were thirst, dry mouth, and pollakiuria or polyuria, consistent with the known mechanism of action of the drug. In these trials, 10% (23/223) of tolvaptan-treated patients discontinued treatment because of an adverse event, compared to 12% (26/220) of placebo-treated patients, with no individual adverse reactions resulting in discontinuation of trial medication at an incidence of >1% in tolvaptan-treated patients.

Clinical Trial Adverse Drug Reactions: *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

In multiple-dose, placebo-controlled trials, 607 hyponatremic patients (serum sodium <135 mEq/L) were treated with SAMSCA, whether in hyponatremic trials or in those that evaluated patients with heart failure. The mean age of these patients was 62 years, with 70% of patients male, and 82% Caucasian. One hundred eighty-nine (189) tolvaptan-treated patients had a serum sodium <130 mEq/L, and 52 patients had a serum sodium <125 mEq/L. Hyponatremia was attributed to cirrhosis in 17% of patients, heart failure in 68% and SIADH/other in 16%. Of these patients, 223 were treated with the recommended dose titration, i.e., 15 mg OD titrated to 60 mg as needed to raise serum sodium.

Table 1 lists the adverse reactions reported in tolvaptan-treated patients with hyponatremia (serum sodium <135 mEq/L) and at a rate at least 2% greater than placebo-treated patients in two 30-day, double-blind, placebo-controlled trials. In these trials, 223 patients were exposed to tolvaptan, starting at a dose of 15 mg once daily, titrated to 30 and 60 mg, as needed to raise serum sodium. Adverse events resulting in death in these trials were 6% in tolvaptan-treated patients and 6% in placebo-treated patients.

Table 1: Adverse Reactions (>2% more than placebo) in Tolvaptan-Treated Patients in Double-Blind, Placebo-Controlled Hyponatremia Trials

System Organ Class MedDRA Preferred Term	Tolvaptan 15 mg/day-60 mg/day (n=223) n (%)	Placebo (n=220) n (%)
Gastrointestinal Disorders		
Dry mouth	28 (13)	9 (4)
Constipation	16 (7)	4 (2)
General Disorders and Administration Site Conditions		
Thirst[a]	35 (16)	11 (5)
Asthenia	19 (9)	9 (4)
Pyrexia	9 (4)	2 (1)
Metabolism and Nutrition Disorders		
Hyperglycemia[b]	14 (6)	2 (1)
Anorexia[c]	8 (4)	2 (1)
Renal and Urinary Disorders		
Pollakiuria or polyuria[d]	25 (11)	7 (3)

The following terms are subsumed under the referenced ADR in Table 1:
[a] polydipsia; [b] diabetes mellitus; [c] decreased appetite; [d] urine output increased, micturition urgency, nocturia.

In a subgroup of patients with hyponatremia (n=475, serum sodium <135 mEq/L) enrolled in a double-blind, placebo-controlled trial (mean duration of treatment was 9 months) of patients with worsening heart failure, the following adverse reactions occurred in tolvaptan-treated patients at a rate at least 2% greater than placebo: mortality (42% tolvaptan, 38% placebo), nausea (21% tolvaptan, 16% placebo), thirst (12% tolvaptan, 2% placebo), dry mouth (7% tolvaptan, 2% placebo), and polyuria or pollakiuria (4% tolvaptan, 1% placebo).

To report an adverse event, contact the medical info line at 1-877-341-9245 or write to: Otsuka Canada Pharmaceutical Inc., 2250 Alfred Nobel Blvd., Saint-Laurent, Quebec H4S 2C9

DRUG INTERACTIONS

(see full listing in Supplemental Product Information section)

Overview: SAMSCA (tolvaptan) is a CYP 3A4 substrate and does not appear to have clinically meaningful inhibitory activity. *In vitro* trials indicated that tolvaptan was extensively metabolized by the cytochrome P450 isoenzyme CYP 3A4/5 and formed many metabolites. The metabolism of most tolvaptan metabolites is also mediated by CYP 3A4/5. There have been no trials performed to determine the potential interaction of tolvaptan with alcohol.

DRUG-FOOD INTERACTIONS

(see full listing of other interactions in Supplemental Product Information section)

Grapefruit Juice: Co-administration of grapefruit juice and SAMSCA results in a 1.8-fold increase in exposure to tolvaptan. Concomitant use should be avoided.

Administration

DOSAGE AND ADMINISTRATION

Dosing Considerations: SAMSCA (tolvaptan) should be initiated, or re-initiated, only in hospital where serum sodium can be monitored closely by physicians experienced in the management of clinically important hyponatremia.

There is no need to adjust dose based on age, gender, race, cardiac or hepatic function. There is no need to adjust the dose in patients with mild to severe renal impairment (creatinine clearance 10-79 mL/min) as there is no increase in exposure to tolvaptan. Tolvaptan has not been evaluated in patients with creatinine clearance <10 mL/min or in patients undergoing dialysis. No benefit can be expected in patients who are anuric.

Recommended Dose and Dosage Adjustment: The usual starting dose for SAMSCA is 15 mg administered once daily without regard to meals. Increase the dose to 30 mg once daily, after at least 24 hours, and then to a maximum of 60 mg once daily, as needed, to achieve the desired level of serum sodium. During initiation and titration, frequently monitor for changes in serum electrolytes and volume. Avoid fluid restriction during the first 24 hours of therapy. Patients receiving SAMSCA should be advised that they can continue ingestion of fluid in response to thirst. Following discontinuation of SAMSCA, patients whose cause of hyponatremia has not been determined should be evaluated for maintenance of acceptable serum sodium levels. Appropriate therapy should be instituted, if needed.

Missed Dose: If a dose is missed, it should be taken as soon as possible. However, if it is near the time of the next dose, only the prescribed dose should be taken. A double dose should not be taken.

Administration: Tolvaptan can be taken without regard to food or the timing of food. It should not be taken with grapefruit juice, or after eating grapefruit, as this may cause a significant increase in tolvaptan concentrations.

OVERDOSAGE:

In healthy subjects, single oral doses of SAMSCA (tolvaptan) of up to 480 mg, and multiple doses up to 300 mg once daily for 5 days have been well tolerated in trials. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect, that is, a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia.

If overdose occurs, estimation of the severity of poisoning is an important first step. A thorough history and details of overdose should be obtained, and a physical examination should be performed. The possibility of multiple drug involvement must be considered.

Treatment should involve symptomatic and supportive care, with respiratory, ECG and blood pressure monitoring, and water/electrolyte supplements as needed. A profuse and prolonged aquaresis should be anticipated, which, if not matched by oral fluid ingestion, should be replaced with intravenous hypotonic fluids, while closely monitoring electrolytes and fluid balance.

ECG monitoring should begin immediately and continue until ECG parameters are within normal ranges. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for human plasma protein (>99%). Close medical supervision and monitoring should continue until the patient recovers.

For management of suspected drug overdose,
consult the regional Poison Control Centre.

Study References

1. Otsuka Canada Pharmaceutical Inc. SAMSCA® (tolvaptan) Product Monograph. July 2011.

Supplemental Product Information

SPECIAL POPULATIONS (continued) **Pregnant Women:** In embryo-fetal development trials, pregnant rats and rabbits received oral tolvaptan during organogenesis. Rats received 2 to 162 times the maximum recommended human dose (MRHD) of tolvaptan (on a body surface area basis). Reduced fetal weights and delayed fetal ossification occurred at 162 times the MRHD. Signs of maternal toxicity (reduction in body weight gain and food consumption) occurred at 16 and 162 times the MRHD. When pregnant rabbits received oral tolvaptan at 32 to 324 times the MRHD (on a body surface area basis), there were reductions in maternal body weight gain and food consumption at all doses, and increased abortions at the mid and high doses (about 97 and 324 times the MRHD). At 324 times the MRHD, there were increased rates of embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations. **ADVERSE REACTIONS** (continued) **Clinical Trial Adverse Drug Reactions: Less Common Clinical Trial Adverse Drug Reactions:** The following adverse reactions occurred in <2% of hyponatremic patients treated with SAMSCA and at a rate greater than placebo in double-blind placebo-controlled trials (n=607 tolvaptan; n=518 placebo) or in <2% of patients in an uncontrolled trial of patients with hyponatremia (n=111), and are not mentioned elsewhere in ADVERSE REACTIONS. **Blood and Lymphatic System Disorders:** disseminated intravascular coagulation **Cardiac Disorders:** intracardiac thrombus, ventricular fibrillation **Gastrointestinal Disorders:** ischemic colitis **Investigations:** Prothrombin Time prolonged **Metabolism and Nutrition Disorders:** diabetic ketoacidosis **Musculoskeletal and Connective Tissue Disorders:** rhabdomyolysis **Nervous System:** cerebrovascular accident **Renal and Urinary Disorders:** urethral hemorrhage **Reproductive System and Breast Disorders (female):** vaginal hemorrhage **Respiratory, Thoracic, and Mediastinal Disorders:** pulmonary embolism, respiratory failure **Vascular Disorder:** deep vein thrombosis **Abnormal Hematologic and Clinical Chemistry Findings:** Clinically significant laboratory test result abnormalities with a potential association with tolvaptan therapy include increased potassium, glucose, sodium, and uric acid. Among these, the only notable difference in change from baseline values was observed for sodium. Only modest differences in these laboratory results have been seen to date with tolvaptan treatment, compared to placebo. **Post-Market Adverse Drug Reactions:** The most common post-marketing events reported with SAMSCA treatment regardless of causality assessment include blood sodium increased, fluid retention, peripheral edema, ear pain, weight loss, dry throat, nasal congestion, cough, septic shock, cardiac failure, hypovolemic shock, and esophageal varices. **DRUG-DRUG INTERACTIONS: Effects of Drugs on Tolvaptan:** ***Ketoconazole and Other Strong CYP 3A Inhibitors:*** SAMSCA is metabolized primarily by CYP 3A. Ketoconazole is a strong inhibitor of CYP 3A and also an inhibitor of P-gp. Co-administration of SAMSCA and ketoconazole 200 mg daily results in a 5-fold increase in exposure to tolvaptan. Therefore, co-administration of SAMSCA with other strong CYP 3A inhibitors (e.g., some macrolides, azole antifungals, protease inhibitors, such as clarithromycin, telithromycin, itraconazole, ritonavir, saquinavir, nelfinavir, nefazodone) would significantly increase urine output and could produce a greater than expected increase in serum sodium. Thus, SAMSCA and strong CYP 3A inhibitors should not be coadministered. ***Moderate CYP 3A Inhibitors:*** The impact of moderate CYP 3A inhibitors (e.g., erythromycin, fluconazole, aprepitant, diltiazem and verapamil) on the exposure to co-administered tolvaptan has not been assessed. A substantial increase in the exposure to tolvaptan would be expected when SAMSCA is coadministered with moderate CYP 3A inhibitors. Co-administration of SAMSCA with moderate CYP 3A inhibitors should therefore generally be avoided. ***P-gp Inhibitors:*** Reduction in the dose of SAMSCA may be required in patients concomitantly treated with P-glycoprotein (P-gp) inhibitors, such as cyclosporine, based on clinical response. ***Rifampin and Other CYP 3A Inducers:*** Rifampin is an inducer of CYP 3A and P-gp. Co-administration of rifampin and SAMSCA reduces exposure to tolvaptan by 85%. Therefore, the expected clinical effects of SAMSCA in the presence of rifampin and other inducers (e.g., rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine and St. John's Wort) may not be observed at the usual dose levels of SAMSCA. The dose of SAMSCA may have to be increased, if such co-administration is to be pursued. ***Lovastatin, Digoxin, Furosemide, and Hydrochlorothiazide:*** Co-administration of lovastatin, digoxin, furosemide, and hydrochlorothiazide with SAMSCA has no apparent clinically relevant impact on the exposure to tolvaptan. **Effects of Tolvaptan on Other Drugs:** ***Digoxin:*** Digoxin is a P-gp substrate, while tolvaptan is a P-gp inhibitor. Co-administration of SAMSCA and digoxin results in a 1.3-fold increase in the exposure to digoxin. ***Warfarin, Amiodarone, Furosemide, and Hydrochlorothiazide:*** Co-administration of tolvaptan does not appear to alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethylamiodarone) to a clinically significant degree. ***Lovastatin:*** SAMSCA is a weak inhibitor of CYP 3A. Co-administration of lovastatin and SAMSCA increases the exposure to lovastatin and its active metabolite, lovastatin-ß hydroxyacid, by factors of 1.4 and 1.3, respectively. This does not appear to be a clinically relevant change. **DRUG-HERB INTERACTIONS:** Interactions with herbal products have not been established. **PHARMACODYNAMIC INTERACTIONS:** Tolvaptan use produces a greater 24-hour urine volume than does furosemide or hydrochlorothiazide. However, concomitant administration of tolvaptan with furosemide or hydrochlorothiazide results in a 24-hour volume that is similar to that after tolvaptan administration alone. Furosemide co-administered with tolvaptan produces a similar maximal rate of urine excretion compared to furosemide alone and 70% higher than tolvaptan alone. HCTZ co-administered with tolvaptan produces a slightly higher maximal excretion rate compared to tolvaptan alone and 66% higher compared to HCTZ alone. Although specific interaction trials were not performed, in clinical trials tolvaptan was used concomitantly with beta-blockers, angiotensin-receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACEI) and/or potassium-sparing diuretics. Adverse reactions of hyperkalemia were approximately 1-2% higher when tolvaptan was administered with ARB, ACEI, and/or potassium-sparing diuretics, compared to administration of these medications with placebo. Serum potassium levels should be monitored during concomitant drug therapy. **DRUG-LIFESTYLE INTERACTIONS:** Interactions with lifestyle parameters have not been established.

Product Monograph available upon request.

Marketed by: Otsuka Canada Pharmaceutical Inc., St. Laurent, Quebec H4S 2C9

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Pr Samsca® (tolvaptan)

Otsuka
Otsuka Canada Pharmaceutical Inc.

Member PAAB R&D

JAP 11/2011 E

NovoRapid®
(insulin aspart)

Professed Standard
Solution for injection

PRESCRIBING SUMMARY

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION
Antidiabetic Agent

INDICATIONS AND CLINICAL USE
NovoRapid® (insulin aspart) is indicated for the treatment of patients with diabetes mellitus who require insulin for the control of hyperglycemia.

NovoRapid® should normally be used in regimens together with an intermediate or long-acting insulin.

NovoRapid® (10 mL vials) may also be used for continuous subcutaneous insulin infusion (CSII) in pump systems which are licensed in Canada for insulin infusion.

Geriatrics (> 65 years of age): There was no clinically relevant difference in the pharmacokinetics and pharmacodynamics of **NovoRapid®** between elderly and younger subjects.

Pediatrics (2 - 17 years of age): Evidence from clinical studies and experience suggests that use in the pediatric population is not associated with any differences in safety or effectiveness.

CONTRAINDICATIONS
NovoRapid® should not be administered during episodes of hypoglycemia or in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

Safety Information

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- Hypoglycaemia is the most common adverse effect of insulin products. As with all insulin products the timing of hypoglycaemia may differ. Glucose monitoring shall be performed for all patients with Diabetes Mellitus treated with insulins
- Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma or even death
- Any transfer of insulin products should be made cautiously and only under medical supervision
- Some insulin products are short-acting insulin and are known for their rapid onset and short duration of action. The injection of such insulin products should immediately be followed by a meal (within 5 to 10 minutes or given immediately after the meal
- Short-acting insulins should be combined with a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control
- Insulin products shall not be mixed with any other insulin unless clearly indicated and done under medical supervision
- Insulin products shall not be used if it is not waterclear and colourless or if it has formed a deposit of solid particles on the wall of the vial or cartridge

General
As with all insulins, the duration of action of **NovoRapid®** may vary in different individuals or in the same individual according to dose, injection site, blood flow, temperature and level of physical activity.

NovoRapid® differs from regular human insulin by its rapid onset and shorter duration of action. As a result of the fast onset of action, the injection of **NovoRapid®** should immediately be followed by a meal. As a result of the short duration of action of **NovoRapid®**, patients with diabetes may also require a longer-acting insulin to maintain adequate glucose control.

Hypokalemia is among the potential clinical adverse effect associated with the use of all insulins therapies. This potential clinical adverse effect may be relevant in patients who are on potassium lowering drugs or losing potassium through other means (e.g. diarrhoea).

Thiazolidinediones (TZDs), alone or in combination with other antidiabetic agents (including Insulin), can cause heart failure and oedema. The combination of Insulin with a TZD is not indicated for the treatment of Type 2 Diabetes Mellitus. Please refer to the respective TZD product monograph WARNINGS AND PRECAUTIONS information when the use of these drugs in combination with any insulin, including **NovoRapid®**, is contemplated.

Endocrine and Metabolism

Hypoglycemia
As with other insulins, hypoglycemia is the most common adverse effect of insulin therapy, including **NovoRapid®**. Such reactions following treatment with **NovoRapid®** are mostly mild and easily managed. While the frequency of hypoglycemia observed in clinical trials is similar to that observed with regular human insulin, clinical trials in patients with type 1 diabetes have demonstrated a reduced risk of nocturnal hypoglycemia with insulin aspart compared with soluble human insulin.

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of **NovoRapid®**. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Patients, whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes. Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement.

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia.

Stress or concomitant illness, especially infectious and febrile conditions may change insulin requirements. In these instances, patients should contact their physician and carefully control their blood glucose. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

Some people may not recognize when their blood sugar drops low.

Glucose monitoring is recommended for all patients with diabetes.

Hyperglycemia
Inadequate dosing or discontinuation of insulin treatment, especially in type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Usually the first symptoms of hyperglycemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hepatic/Biliary/Pancreas
As with other insulins, **NovoRapid®** requirement may need to be adjusted in patients with hepatic impairment.

Immune

Local Allergic Reaction
As with any insulin therapy, injection site reactions may occur and include pain, redness, itching, hives, swelling, bruising and inflammation. On rare occasions, injection site reactions may require discontinuation of **NovoRapid®**.

Systemic Allergic Reaction
Systemic allergic reactions have not been reported during the clinical development of **NovoRapid®**. Systemic allergic reactions have rarely occurred with **NovoRapid®** as with other insulin treatment. Severe cases of generalized allergy including anaphylactic reaction may be life threatening.

Antibody Production
Immune responses can occur in response to insulin. This may be associated with elevated IgG levels, however this does not appear to affect HbA1c.

Renal
The degree of renal impairment does not affect the pharmacokinetics variable of **NovoRapid®**. As with other insulins, **NovoRapid®** requirement may be reduced in patients with renal impairment. **NovoRapid®** requirement may need to be adjusted in patients with severe renal impairment.

Sexual Function/Reproduction
There is no information on teratogenicity of **NovoRapid®** in humans.

Pregnancy
Congenital anomalies are three to four times more prevalent in diabetic pregnancy than in non-diabetic pregnancies and with a two fold higher mortality from major cardiovascular anomalies.

Special Populations
Pregnant Women: NovoRapid® can be be used in pregnant women with type 1 diabetes if clinically indicated. It is essential for patients with type 1 diabetes to maintain good metabolic control before conception and throughout pregnancy. Patients should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control is essential in these patients.

Nursing Women: It is unknown whether **NovoRapid®** is excreted in significant amounts in human milk. For this reason, caution should be exercised when **NovoRapid®** is administered to a nursing mother.

Geriatrics: Careful glucose monitoring and individual dose adjustments of insulin, including insulin aspart, may be necessary in elderly patients.

Transferring Patients from Other Insulins:
When patients are transferred between different types of insulin products, including animal insulins, the early warning symptoms of hypoglycemia may have changed or become less pronounced than those experienced with their previous insulin. Transferring a patient to a new type or brand of insulin should be done only under strict medical supervision. Changes in insulin strength, timing of administration, manufacturer, type (e.g. regular, NPH or insulin analogs), or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage. Concomitant oral anti-diabetic treatment may also need to be adjusted. If an adjustment is needed, it may be done with the first doses or during the first weeks or months and under medical supervision.

Mixing of Insulins:
Mixing of on insulin formulation with another insulin formulation may change the pharmacokinetic and/or

pharmacodynamic profile of action of the combined mixture in an unpredictable matter. (see DOSAGE AND ADMINISTRATION)

If **NovoRapid®** (insulin aspart) is mixed with an intermediate-acting or long-acting insulin, **NovoRapid®** should be drawn into the syringe first. The injection should be made immediately after mixing. Pharmacodynamic trials conducted in pigs showed bioequivalence between separate injections of **NovoRapid®**. These included neutral protamine regular human insulin, a mix of **NovoRapid®** and neutral protamine regular human insulin when injected 5 minutes after mixing.

The effects of mixing **NovoRapid®** with either animal-source insulins or human insulin preparations produced by other manufacturers have not been studied. This practice is not recommended.

Monitoring and Laboratory Tests

As with all insulin therapy, the need for regular blood glucose self-monitoring should be considered when using **NovoRapid®** to obtain optimal glycemic control. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control. If a patient is pregnant, careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

ADVERSE REACTIONS

Adverse Drug Reaction Overview: Adverse reactions observed in patients using **NovoRapid®** are mainly due to the pharmacologic effect of insulin. The most frequently seen undesirable effect in insulin-treated patients is change in blood glucose levels. From clinical investigations, it is known that major hypoglycaemia, defined as need for assistance in treatment, is common (>1/10) in well-controlled patients. Based on post-marketing experience adverse events including hypoglycaemia are rare (>1/10 000 and <1/1000) during use of Novo Nordisk human insulin products.

To report an adverse event, contact the Canada Vigilance Program Monitoring Office at 1-866-234-2345 or contact Novo Nordisk Canada Inc., 300-2680 Skymark Avenue, Mississauga, ON, L4W 5L6, Telephone: 905-629-4222 or 1-800-465-4334.

DRUG INTERACTIONS

Overview

As with insulin in general, concomitant use of other drugs may influence insulin requirements.

Administration

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients being initiated on insulin can be started on **NovoRapid®** in the same manner as they would be on animal-source or human insulin
- Changes for patients being transferred from other insulin to **NovoRapid®** should be made as directed by a physician
- In clinical trials, patients were transferred on a unit to unit basis from Novolin®**ge** Toronto to **NovoRapid®**. The doses of meal-related and basal insulin were then changed according to the patients' needs and local practice

Recommended Dose and Dosage Adjustment

Due to its faster onset of action, **NovoRapid®** should be given immediately before the meal. The injection should not be more than 5-10 minutes before the start of a meal. When necessary, **NovoRapid®** may be given immediately after the meal.

Dosage of **NovoRapid®** is individual and determined, based on the physician's advice, in accordance with the needs of the patient. The individual insulin requirement is usually between 0.5 - 1.0 units/kg/day. In a meal-related treatment, 50 - 70% of this requirement may be provided by **NovoRapid®** and the remainder provided by an intermediate-acting or long-acting insulin.

Administration

NovoRapid® (insulin aspart) is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should be rotated within the same region. **NovoRapid®** retains its more rapid onset and shorter duration of action irrespective of the injection site used (abdomen, thigh, upper arm). As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Study References

1. **NovoRapid®** Product Monograph. Novo Nordisk Canada Inc. December 8, 2011.

SUPPLEMENTAL PRODUCT INFORMATION

WARNINGS AND PRECAUTIONS

Endocrine and Metabolism

Hypoglycemia

Hypoglycemia can occur regardless of what type of insulin you take and can cause fatigue, sweating, heart palpitations, disturbed behaviour, hunger, convulsions, loss of consciousness or, in extreme circumstances, even death which can occur without recognizable symptoms.

Special Populations

Pregnant Women: Insulin requirements usually decrease during the first trimester and increase during the second and third trimesters.

Nursing Women: Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan or both.

Others: The presence of diseases such as Acromegaly, Cushing's syndrome, Hyperthyroidism and Pheochromocytoma can complicate the control of diabetes mellitus.

Immune

Local allergic reaction

Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks.

Systemic Allergic Reaction

These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing and drop in blood pressure.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

The safety profile of **NovoRapid®** observed in clinical trials is similar to the safety profile reported for Novo Nordisk human insulin products.

Frequencies of adverse drug reactions from clinical trials, which by an overall judgement are considered related to **NovoRapid®** are listed below. The frequencies are defined as: Uncommon (>1/1,000, <1/100) and rare (>1/10,000, <1/1,000). Isolated spontaneous cases are presented as very rare defined as (<1/10,000).

Immune system disorders:

Uncommon: Urticaria, rash, eruptions

Very Rare (>1/10 000, <1/1000): Anaphylactic Reactions: Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening.

Nervous system disorders:

Rare: Peripheral neuropathy: Fast improvement in blood glucose control may be associated with a condition termed acute painful neuropathy, which is usually reversible.

Eye disorders:

Uncommon: Refraction disorder: Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Uncommon: Diabetic retinopathy: Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders:

Uncommon: Lipodystrophy: May occur at the injection site as a consequence of failure to rotate injection sites within an area.

Uncommon: Local hypersensitivity: Reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

General disorders and administration site conditions:

Uncommon: Oedema: May occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Post-Market Adverse Drug Reactions:

Adverse Drug Event Overview for a Post-Marketing CSII Trial

A 4 month post-marketing study in 511 subjects with type 1 and insulin-requiring type 2 diabetes mellitus was conducted as a preference trial to assess the treatment satisfaction of **NovoRapid®** and insulin lispro during CSII pump therapy. Adverse drug events were recorded when spontaneously reported by the patients in the study. The only adverse drug event reported at an incidence ≥ 1% was upper respiratory tract infection (incidence of 1.3% in the **NovoRapid®** group).

Less Common Adverse Drug Events (<1%) in a Post-Marketing CSII Trial

In addition, the following adverse drug events were reported at an incidence of <1% for **NovoRapid®** or insulin lispro in this study (in more than 1 patient in each treatment group), regardless of drug relationship.

Gastrointestinal Disorders: vomiting, nausea

Infections and Infestations: viral infection, urinary tract infection, sinusitis, onychomycosis, nasopharyngitis, bronchitis

Metabolism and Nutrition Disorders: hypoglycemia, hyperglycemia, diabetic ketoacidosis

Musculoskeletal and Connective Tissue Disorders: pain in extremity, back pain, arthralgia

Nervous System Disorders: neuropathy

Respiratory, Thoracic and Mediastinal Disorders: nasal congestion

DRUG INTERACTIONS

Drug-Drug Interactions

The following substances may reduce the insulin requirements: Oral antidiabetic drugs, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids, sulhonamides and alcohol.

The following substances may increase insulin requirements: Oral contraceptives, thiazides, glucocorticosteroids, thyroid hormones, sympathomimetics growth hormone and danazol.

Beta blocking agents may mask the symptoms of hypoglycemia and delay recovery from hypoglycemia.

Octreotide/lanreotide may either increase or decrease insulin requirements.

To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with **NovoRapid®** is not indicated.

Drug-Lifestyle Interactions

Patients should be informed about potential advantages and disadvantages of **NovoRapid®** (insulin aspart) therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, lifestyle management, self-monitoring, complications of insulin therapy, timing of dosage, instruction for use of injection devices and storage of insulin.

The need for regular blood glucose self-monitoring should be considered when using **NovoRapid®** to obtain optimal glycemic control.

Alcohol may intensify or reduce the hypoglycemic effect of insulin.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The dosing of **NovoRapid®** should regularly adjusted according to blood glucose measurements. Adjustment dosage may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycemia.

Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use **NovoRapid®** if it has become viscous (thickened) or cloudy; use it only if it is clear and colourless. **NovoRapid®** should not be used after its expiration date.

If **NovoRapid®** is mixed with an intermediate-acting or long-acting insulin, **NovoRapid®** should be drawn into the syringe first. The injection should be made immediately after mixing. **NovoRapid®** should not be mixed with long-acting insulin analogue. The effect of mixing **NovoRapid®** with either animal-source insulins or human insulin preparations produced by other manufacturers have not been studied. This practice is not recommended.

In patients with diabetes mellitus, optimized metabolic control effectively delays the onset and slows the progression of late diabetic complications. Optimized metabolic control, including glucose monitoring is therefore recommended.

NovoRapid® (10 mL vial) may be used for Continuous Subcutaneous Insulin Infusion (CSII) in pump systems licensed for insulin infusion. Patients using CSII should be comprehensively instructed in the use of the pump system. The infusion and reservoir set should be changed according to the pump manufacturer's instructions. Patients administering **NovoRapid®** by CSII must have an alternate insulin delivery device available in case of pump system failure.

Before travelling between different time zones the patient should seek the doctors' advice since this means that the patient has to take the insulin and meals at different times.

As a precautionary measure, patients should carry a spare syringe and extra insulin in case the insulin delivery device is lost or damaged.

HYPOGLYCEMIA AND OVERDOSAGE

Hypoglycemia may occur as a result of an excessive dose of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia. Symptoms of hypoglycemia may occur suddenly. They may include cold sweat, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may be fatal.

Mild episodes of hypoglycemia can be treated by oral administration of glucose or sugary products. It is therefore recommended that patients with diabetes always carry some sugar candy.

Severe hypoglycemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person or glucose given intravenously by a medical professional. Glucose must also be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of an oral carbohydrate is recommended for the patient in order to prevent relapse.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Complete Product Monograph available upon request.

Novo Nordisk Canada Inc., 200-2680 Skymark Avenue, Mississauga Ontario, L4W 5L6, 905-629-4222 or 1-800-465-4334.

www.novonordisk.ca

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Janumet®

(sitagliptin phosphate monohydrate
and metformin hydrochloride)

Januvia®

(sitagliptin phosphate monohydrate)

For more information on **JANUMET®** and **JANUVIA®**, please contact our Customer Information Centre at **1-800-567-2594** or your local representative.

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