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LETTER FROM THE EDITOR

Dear readers:

I am very pleased to present you with four articles in this second edition of *ReFlections* for 2014. The first article is written by Dr. Dave Rengachary, who draws upon his training as a neurologist to discuss advances in multiple sclerosis. His insights should be valuable in helping understand the current investigative modalities, classification and treatment of this important disorder.

The second article has been written by Dr. Kamran Khan, who has very recently entered into a formalized consulting relationship with RGA. Dr. Khan is the founder of BioDiaspora, an organization that seeks to understand the complex relationship between global travel, human migration, and infectious diseases. He is an infectious disease clinician and scientist based in Toronto, with ties to multiple health organizations in the U.S. and around the world. RGA's relationship with Dr. Khan

allows us to draw on his expertise regarding infectious diseases such as MERS, pandemic influenzas and, most recently, Ebola. His contributory article discusses infectious diseases in general, with more specific discussion on the recent MERS epidemic occurring in the Middle East. Dr. Khan is currently providing us with information and opinions on emerging threats such as Ebola and the potential for widespread antibiotic resistance of bacterial infections.

The third article in *ReFlections* has been provided by Dr. Paul Davis, who provides us with a thorough overview of Sudden Cardiac Death, with a focus on Brugada syndrome. This relatively rare, but extremely serious, impairment is discussed at length. The information in his article will help all of us recognize the EKG patterns associated with the condition and fully appreciate the risk associated with it.

The final article for this edition has been provided by Jeffrey Heaton, who is a member of the team of RGA associates tasked with reviewing developments in electronic health records and considering their impact on the insurance industry. In his article, he introduces us to SNOMED-T (Systematized Nomenclature of Medicine for Clinical Terms).

I hope that you enjoy all of these articles and as always please feel free to contact us with comments or questions about any of these articles.

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ADVANCES IN MULTIPLE SCLEROSIS

By Dave Rengachary M.D.

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Perhaps no other field of neurology has seen as rapid and promising developments as multiple sclerosis.

Projected improvements in mortality must be tempered by unique risks associated with new treatment modalities. Increasingly sensitive diagnostic tools, changing criteria, and trends toward treatment earlier in disease course will have a significant impact on critical illness assumptions. The purpose of this article is therefore to review changes in diagnostic criteria, emerging concepts in demyelinating variants, new imaging modalities, and a wave of new pharmacologic treatments.

Background

Multiple sclerosis (MS) is the prototypical autoimmune chronic demyelinating disorder. According to the recently released *Atlas of Multiple Sclerosis*,¹ there are 2.3 million people living worldwide with the disease corresponding to a prevalence of 33 per 100,000. There are roughly 400,000 people in the United States with the disorder. The average age of onset is 30 years with a well-described and stable 2:1 female to male ratio. The previous 2008 report estimated global incidence at 2.5 per 100,000.² An interesting and unique epidemiologic feature of MS is the decreasing prevalence rates closer to the equator, supporting emerging theories highlighting the role of Vitamin D (and sunlight) in the disorder. The ultimate etiology remains hotly debated. Most current pathophysiologic theories center around a combination of genetic susceptibility factors and environmental influences such as viral exposures. The end result is repeated demyelinating attacks on the axons of the brain and spinal cord, followed by remyelination and corresponding clinical improvement, almost certainly partial in nature. While multiple sclerosis is classically thought of as a demyelinating white matter disorder, increasing emphasis is being placed upon axon loss in the disorder, grey-matter involvement, and subsequent prognostic implications.

Diagnostic Criteria

The initial challenge in multiple sclerosis remains accurate diagnosis as there is no single ‘gold standard’ diagnostic tool that offers complete certainty, especially early on in disease course. Accordingly, several criteria have been developed to solidify diagnosis. Originally developed in 2001, the McDonald criteria have garnered widest acceptance over time. The criteria have undergone major revisions in 2005 and in 2010. Of interest to the critical illness industry, with each revision, the criteria have become less ‘stringent’ in terms of objective radiographic and clinical

requirements necessary to satisfy the diagnosis. At its core, the criteria remain centered about the oft-repeated “dissemination in time and space” (see Figure 1).

Dissemination In Space – One or more characteristic MS lesions in at least two of the following locations:

- Periventricular
- Juxtacortical
- Infratentorial
- Spinal Cord

Dissemination in Time

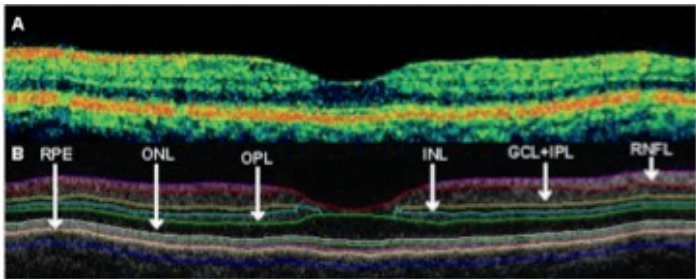
- A new characteristic enhancing and/or non-enhancing lesion on MRI in comparison with a baseline scan performed.
- Any combination of non- enhancing and asymptomatic enhancing MRI lesions on the same scan.

Key updates with Revised 2010 McDonald criteria.³

- Reduction in the number of MS lesions required to satisfy definition of Dissemination in Space. This can now be satisfied with a *minimum of two lesions*.
- Removal of 30-day time period previously required between first clinical attack and MRI of the brain to satisfy Dissemination in Time criteria.
- In some cases, Dissemination in Time may now be satisfied *with a single scan*.
- Removal of CSF studies from DIS definition, further de-emphasizing their importance.

Developments in Imaging

Optical Coherence Technology



(Tátrai, E. et al, PLoS ONE (2012) Creative Commons Attribution (CC BY) license).¹²

Optical Coherence Technology (OCT) is an increasingly utilized high-resolution form of computed tomography for the detection of retinal and optic nerve disorders. Infrared light is typically used to reconstruct the macular and peripapillary areas, producing an image reminiscent of B mode ultrasound.⁴ With a resolution of 5-7 micrometers

Fig. 1 – 2010 McDonald Criteria for Diagnosis of Multiple Sclerosis

Clinical Episodes	Objective Clinical Lesions	Additional Requirements to Satisfy Diagnosis
2 or more	2 or more	None
2 or more	1	Dissemination in Space (either by MRI or CSF or second clinical attack)
1	2	Dissemination in Time (either by MRI or second clinical attack)
1	1	Dissemination in Space and Time (Either by MRI or second clinical attack)
0/Progressive at Onset	N/A	One year of disease progression and 2/3 of the following: <ul style="list-style-type: none">▪ DIS in brain▪ DIS in Spinal cordpositive CSF

it has been described as providing a near “in vivo ‘optical biopsy’” of the areas of interest.⁵ In equivocal, remote, or retrobulbar (i.e., not detectable by direct ophthalmoscope) cases of optic neuritis, OCT can provide an objective and accurate measurement of retinal nerve fiber layer thickness. As discussed below, patients on Fingolimid (Gilenya) must be monitored for the development of macular edema, which can also be detected with this technology. Interestingly, axon loss in multiple sclerosis has been well demonstrated in the absence of clinical optic neuritis, thus prompting interest as a measure of overall disease activity and prognosis. OCT has not however been found to predict progression from isolated optic neuritis to clinically definite multiple sclerosis.

Advanced MRI techniques

Several MRI techniques under refinement will only increase the sensitivity and advance the timeline for detection of multiple sclerosis lesions. Magnetization transfer imaging (MTI) relies on the detection of decreased proton binding to macromolecules seen preferentially in early demyelinating lesions. This technique has generated interest as a more sensitive finding of both demyelination and remyelination than current gadolinium Enhancement. Diffusion Tensor Imaging (DTI) is able to detect abnormal directions of the diffusion of water molecules in MS lesions and has demonstrated clear abnormalities in white matter axon tracts which would have been considered normal with standard MRI techniques. Finally, Double Inversion Recovery (DIR) images, as the name implies, use two inversion pulses to differentiate with greater sensitivity cortical lesions (grey matter) from background white matter and cerebrospinal fluid.⁶

Selected Demyelinating Variants

Clinical Isolated Syndrome

Clinically Isolated Syndrome (CIS) refers to a single clinical demyelinating event which then places the patient at higher risk for future development of clinically definite multiple sclerosis (CDMS). Underwriters should therefore be aware of the overall risk of progression to clinically definite multiple sclerosis as well as the prognostic factors which may significantly alter this risk. Estimates of the overall risk of developing multiple sclerosis vary widely depending upon cohorts and timeframes studied, but is generally quoted at 50% within the next five years.⁸ Not surprisingly, the most important prognostic factor is often the MRI performed at the time of the clinical event. According to the National Multiple Sclerosis Society in the U.S., the risk of developing multiple sclerosis with a “positive” MRI for characteristic demyelinating lesions is between 60% and 80%.⁹ If MRI is normal at the time of the initial event, the risk drops to 20%.

Numerous studies^{8,10,11} have attempted to delineate further factors influencing the odds of progression to clinically definite multiple sclerosis. For ease these can be divided in to “favorable” and “unfavorable” factors (Figure 2).

Figure 2. Favorable and Unfavorable factors affecting risk of progression from CIS to CDMS

Favorable	Unfavorable
<ul style="list-style-type: none"> • Normal MRI • Isolated optic neuritis • Isolated Sensory Symptoms • Normal CSF • Caucasian • Age > 30 • Unifocal symptoms at onset • Low EDSS (Expanded Disability Status Scale) 	<ul style="list-style-type: none"> ▪ “Positive” MRI at presentation ▪ Motor symptoms ▪ Excess Oligoclonal bands in cerebrospinal fluid in comparison to serum (and other CSF markers to a lesser extent) ▪ Abnormal Evoked Potential Studies ▪ Non-White ▪ Age < 30 ▪ Multifocal symptoms at onset ▪ High EDSS (Expanded Disability Status Scale) ▪ Smokers ▪ Positive Epstein Barr Virus (EBV) Titers ▪ Spinal Cord Lesions/Transverse Myelitis

An important trend in the management of CIS is the shift toward treatment of a single demyelinating event with Disease Modifying Therapies (DMTs) previously reserved for CDMS. This reflects the findings of several key trials in CIS. The Controlled High Risk Avonex Multiple Sclerosis Study (CHAMPS) compared interferon beta 1a (Avonex) and placebo in a population of patients with CIS and at least two MRI lesions. The overall probability of developing CDMS was 35% in the interferon beta 1a group versus 50% in the placebo group at three years, a statistically significant difference (P=0.02).^{13,14} The Early Treatment of Multiple Sclerosis (ETOMS) trial compared weekly interferon beta 1a (Rebif) with placebo in patients with CIS who met certain MRI criteria. The primary endpoint was time to CDMS: 569 days for interferon beta 1a versus 252 days for placebo (p = 0.034).¹³ In the BENEFIT Study (Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment), CIS patients were randomized to receive Interferon beta 1b (Betaseron) or placebo. At the end of two years, 28% of patients treated with DMT met criteria for CDMF versus 45% receiving placebo (p < 0.001)¹⁴ Finally, the Presenting With a Clinically Isolating Syndrome (PRECISE) assessed treatment with glatiramer acetate (Copaxone) versus placebo those patients with a combination of CIS and abnormal MRI, finding a 45% relative risk reduction in conversion rates to CDMS (p = 0.0005) by the end of the three-year study. Combining the results of these relatively short-term studies with similarly favorable extension studies has provided relative consensus favoring treatment of CIS (and abnormal MRI) with standard disease-modifying therapies. It can be anticipated that those evaluating critical illness claims will

have to navigate an increasing population of claimants who do not yet meet formal criteria for CDMS but bear the same burden of injectable disease modifying treatments. It can be anticipated that those evaluating critical illness claims will have to navigate an increasing population of claimants who do not yet meet formal criteria for CDMS but bear the same burden of injectable disease modifying treatments.

Neuromyelitis Optica (NMO)

Neuromyelitis Optica or “Devic’s Disease”, merits special attention as a demyelinating variant given recent advancements in the detection and understanding of its underlying pathology. NMO is increasingly thought of not as a single disorder but as a spectrum of disease unified by a combination of prominent spinal cord involvement and bilateral optic neuritis. The disorder differs from multiple sclerosis in several distinct ways. While individual attacks are often treated with intravenous methylprednisone (similar to MS), traditional DMTs have not been found to be helpful as primary maintenance therapy in NMO. In fact, several reports suggest that interferon beta agents may have an exacerbating effect on disease course. Common immunosuppressive agents utilized include Imuran, mycophenolate, and rituximab. In addition to corticosteroids, plasmapheresis is often attempted for aggressive or refractory clinical attacks. Further establishing NMO as a separate disorder was the discovery of specific associated antibodies to aquaporin-4 (AQP4) proteins located in the channels of the foot processes of astrocytes. With sensitivities and specificities estimated at 70% and 90% respectively,¹⁵ this commercially available serology has become a cornerstone of diagnosis. Finally, and perhaps most importantly, NMO is distinguished by a significantly worse prognosis than multiple sclerosis, although mortality estimates vary widely. In one of the largest series, Wingerchuk et al.¹⁶ reported a five-year survival rate of 68% for those with the more common relapsing form of the disease. In contrast, five-year survival rates for the monophasic form of the disease (maximal symptoms within one month of presentation) have been reported to be 90%.¹⁷

Newly Approved Therapies

September 2010 represented a revolution in the care of multiple sclerosis patients, with the approval of Fingolimid (Gilenya) by the U.S. FDA, the first oral disease-modifying therapy. Since that time, two other oral medications have been approved as maintenance therapy, Teriflunomide (Aubagio) and Dimethyl Fumarate (Tecfidera).

Fingolimid

Fingolimid acts as a sphingosine 1 phosphate receptor modulator. Although the exact mechanism is unclear, it is believed that binding of the compound to the receptor blocks the migration of lymphocytes from lymph nodes to

the central nervous system, thus reducing the autoimmune response of multiple sclerosis. Two pivotal phase III trials prompted approval of fingolimid in multiple sclerosis. In the FREEDOMS study (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis), fingolimid was compared with placebo. Fingolimid met the primary endpoint, a reduction in the annual relapse rate (0.16 for fingolimid versus 0.40 for placebo, $p < 0.01$), correlating to a 60% relative reduction. Secondary endpoints of time to disability progression and MRI lesion burden (the number of gadolinium enhancing lesions) were also met.¹⁸ Fingolimid was also compared with interferon beta 1a in the Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS) study. Annualized relapse rate again was the primary endpoint and was significantly lower in the 0.5 mg fingolimid group (0.16) versus interferon beta-1a (0.33, $p < 0.01$). Statistically significant differences in MRI lesions were also found but there was no significant difference in disability progression, likely secondary to a low rate overall of disability progression in both groups.¹⁹

Despite this promising data, several important side effects have emerged from analysis of fingolimid studies. Though rare, cardiac adverse events have been noted, particularly with the first dose. In the two previously mentioned studies, the rates of first-degree AV block and mobitz type I AV blocks were estimated to be 4.7% and 0.2 respectively.²⁰ After report of a first-dose cardiac death on the medication, it is recommended that patients be monitored in the office for six hours after initially receiving the medication. Patients with cardiac comorbidities are often monitored overnight in a hospital setting. An additional unique concern with the medication is macular edema. Again, although rare (0.2 to 1.1% depending on fingolimid dose),²⁰ it is recommended that patients have ophthalmology exams (often utilizing the previously mentioned OCT technology) prior to the medication and for several months thereafter to detect this condition. Finally, there have been case reports of fatal herpes encephalitis, Progressive Multifocal Leukoencephalopathy (PML), and Varicella Zoster (VZV) in association with the medication though causality is controversial.

Teriflunomide

Teriflunomide was FDA approved for the treatment of multiple sclerosis in September of 2012. The oral medication's mechanism of action in multiple sclerosis is unclear, although it is known to block pyrimidine synthesis. In the first phase III study, Teriflunomide Multiple Sclerosis Oral Trial (TEMPO), teriflunomide reduced the annual relapse rate in comparison to placebo (0.37 teriflunomide versus 0.54 placebo, $p < 0.001$). At higher doses (14 mg) further

improvements were seen in disease progression rates and MRI metrics.²¹ In a subsequent comparison with interferon beta 1a, the Teriflunomide and Rebif (TENERE) Trial, there was no statistically significant difference between teriflunomide and interferon beta 1a in the somewhat unusual primary endpoint of treatment failure (defined as either relapse or discontinuation). The medication does come with two 'black box' warnings: 1) Increased ALT levels are described in roughly 14% of cases²² with case reports of liver failure. This prompted recommendations to avoid the medication in those with pre-existing liver disease and follow levels for six months for all others. 2) The medication is contraindicated in woman of childbearing age, given reports of teratogenicity in animal models.

Dimethyl fumarate

Dimethyl fumarate is an oral compound also known by its previous name, BG-12. A chemically related compound has been used for several years to treat psoriasis. Once again, the exact mechanism of the medication remains unclear, but given its role in the activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, an anti-oxidative and neuroprotective pathway has been proposed. Dimethyl Fumarate was FDA approved for the treatment of multiple sclerosis based on two randomized controlled phase III studies, the DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in RRMS) and CONFIRM (Comparator and an Oral Fumarate in RRMS) studies. In the DEFINE study, dimethyl fumarate was compared with placebo; the primary endpoint was the percentage of patient who experienced a relapse at two years. This proportion was significantly lower with dimethyl fumarate than placebo (27% versus 46%, $p < 0.01$) corresponding annualized relapse rates of 0.17 and 0.36 respectively.²³ In the CONFIRM study, dimethyl fumarate and a common injectable, glatiramer acetate (Copaxone), were compared with placebo. This study confirmed superiority over placebo (annual relapse rate 0.20 dimethyl fumarate versus 0.40 placebo, $p < 0.001$), which was the primary design goal. Subsequent analysis, however, did not show a statistically significant difference between dimethyl fumarate and glatiramer acetate.²⁴ Case reports of PML have been described in association with dimethyl fumarate and other fumarate compounds both in patients with multiple sclerosis and psoriasis. Lymphopenia is common with the medication: the pattern is a 30% drop in the first year followed by stabilization; therefore, it is recommended that complete blood cell counts be followed while on therapy. Rates of serious infection however have not been found to be more common on the medication.²⁵

Alemtuzumab

Alemtuzumab was approved in Europe in September 2013 as a first-line agent in the treatment of multiple sclerosis.

A few months later, the FDA rejected approval in the medication in a surprising and controversial decision (the medication had previously been granted fast-track designation). Appeal of the rejection is ongoing. The medication is a monoclonal antibody directed against the CD52 antigen which results in significant and prolonged lymphocyte depletion. One potentially very appealing aspect of the medication is its dosing schedule. In trials it was administered as a single five-day intravenous infusion followed by a three-day infusion one year later. In the CARE MS I trial alemtuzumab was compared with interferon beta 1a. Primary endpoint points were relatively aggressively chosen: an improved relapse rate in comparison with interferon beta 1a (generally considered to be 'strongest' injectable disease modifying therapy) and six-month disability scores. The medication was able to meet the first primary endpoint (annualized relapse rates 0.18 for alemtuzumab and 0.39 for interferon beta 1a, $p < 0.0001$) but not the second.^{26,27} The subsequent CARE MS II trial showed similar findings in a cohort of patients who had failed previous disease modifying therapies.²⁸ The rejection by the FDA was based upon concerns with study design but also safety concerns, in particular a high rate of autoimmune disorders. In pooled analysis autoimmune thyroid complications were seen in 18% of patients, 21 cases of ITP and four cases of glomerulonephritis.²⁹

Conclusion

The landscape of multiple sclerosis is changing. Patients are being diagnosed and treated earlier, with a much wider range of options. Long-term data on these agents is lacking both in terms of mortality and adverse events. Prospects for mortality improvements however are auspicious given initial data on relapse rates and MRI lesion burdens with newly approved agents. Compliance rates are expected to significantly improve with (for many) the replacement of injectables with oral therapies. Moreover, the increasing range of options will likely lower the threshold for changing the regimen of a patient who is relapsing on current therapies. Combinations of therapies may provide additional benefit but this is being navigated cautiously given that most cases of Progressive Multifocal Leukoencephalopathy (PML) have occurred in patients on multiple immunomodulatory agents. Accurate diagnosis, a highly tailored approach, and disease remission remain paramount goals. ■

Selected References

- Multiple Sclerosis International Federation. Atlas of Multiple Sclerosis 2013: Mapping Multiple Sclerosis Around the World. London, England: Multiple Sclerosis International Federation, 2013: http://www.msif.org/includes/documents/cm_docs/2013/m/msif-atlas-of-ms-2013-report.pdf?f=1
- World Health Organization and Multiple Sclerosis International Foundation. Atlas Multiple Sclerosis Resources in the world 2008. Geneva, Switzerland: World Health Organization and Multiple Sclerosis Foundation, 2008: http://www.who.int/mental_health/neurology/Atlas_MS_WEB.pdf
- Katz Sand, Ilana B., and Fred D. Lublin. "Diagnosis and Differential Diagnosis of Multiple Sclerosis." *CONTINUUM: Lifelong Learning in Neurology* 19 (August 2013): 922–43.
- Bermel, Robert A, and Laura J Balcer. "Optic Neuritis and the Evaluation of Visual Impairment in Multiple Sclerosis." *Continuum (Minneapolis, Minn.)* 19, no. 4 Multiple Sclerosis (August 2013): 1074–86.
- Adhi, Mehreen, and Jay S. Duker. "Optical Coherence Tomography - Current and Future Applications." *Current Opinion in Ophthalmology* 24, no. 3 (May 2013): 213–21.
- Klawiter, Eric C. "Current and New Directions in MRI in Multiple Sclerosis." *Continuum (Minneapolis, Minn.)* 19, no. 4 Multiple Sclerosis (August 2013): 1058–73.
- Andreasson, Elisabeth (2012). Neuroimaging in Multiple Sclerosis, Neuroimaging - Clinical Applications, Prof. Peter Bright (Ed.), ISBN: 978-953-51-0200-7, InTech, pp. 317-354.
- "Clinically Isolated Syndrome Fact Sheet" www.ms-trust.org. uk MS Trust. n.d.
- "Clinically Isolated Syndrome" [www.nationalmssociety.org/What-is-MS/Related-Conditions/Clinically-Isolated-Syndrome-\(CIS\)](http://www.nationalmssociety.org/What-is-MS/Related-Conditions/Clinically-Isolated-Syndrome-(CIS)) n.d.
- Marcus, Jacqueline F., and Emmanuelle L. Waubant. "Updates on Clinically Isolated Syndrome and Diagnostic Criteria for Multiple Sclerosis." *The Neurohospitalist* 3, no. 2 (April 2013): 65–80.
- Cree, B. "Clinically Isolated Syndrome: Evaluation, Risk Stratification, and Treatment Decisions." *Johns Hopkins Advanced Studies in Medicine*. Aug2008, Vol. 8 Issue 8, p257-265
- Tátrai, Erika, Magdolna Simó, Anna Iljicsov, János Németh, Delia Cabrera DeBuc, and Gábor Márk Somfai. "In Vivo Evaluation of Retinal Neurodegeneration in Patients with Multiple Sclerosis." *PLoS ONE* 7, no. 1 (January 26, 2012)
- Connor CS, Smith VC. In: Thrower BT and Tullman MJ, eds. *Clinician's Primer on Multiple Sclerosis: Clinically Isolated Syndrome*. Littleton, CO: Medical Education Resources, Inc; 2010:34.
- Beck, Roy W., et al. "Interferon B-1a for Early Multiple Sclerosis: CHAMPS Trial Subgroup Analyses." *Annals of Neurology* 51, no. 4 (April 1, 2002): 481–90.
- Wingerchuk, Dean M., and Brian G. Weinshenker. "Acute Disseminated Encephalomyelitis, Transverse Myelitis, and Neuromyelitis Optica." *CONTINUUM: Lifelong Learning in Neurology* 19 (August 2013): 944–67.
- Wingerchuk, D M, W F Hogancamp, P C O'Brien, and B G Weinshenker. "The Clinical Course of Neuromyelitis Optica (Devic's Syndrome)." *Neurology* 53, no. 5 (September 22, 1999): 1107–14.
- Wingerchuk, D M. "Neuromyelitis Optica." *International MS Journal / MS Forum* 13, no. 2 (May 2006): 42–50.
- Kappos, Ludwig, Ernst-Wilhelm Radue, Paul O'Connor, Chris Polman, Reinhard Hohlfeld, Peter Calabresi, Krzysztof Selmaj, et al. "A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis." *New England Journal of Medicine* 362, no. 5 (2010): 387–401.
- Cohen, Jeffrey A., Frederik Barkhof, Giancarlo Comi, Hans-Peter Hartung, Bhupendra O. Khatri, Xavier Montalban, Jean Pelletier, et al. "Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis." *New England Journal of Medicine* 362, no. 5 (2010): 402–15.
- Willis, Mary A, and Jeffrey A Cohen. "Fingolimod Therapy for Multiple Sclerosis." *Seminars in Neurology* 33, no. 1 (February 2013): 37–44.
- O'Connor, Paul, Jerry S. Wolinsky, Christian Confavreux, Giancarlo Comi, Ludwig Kappos, Tomas P. Olsson, Hadj Benzerdjeb, et al. "Randomized Trial of Oral Teriflunomide for Relapsing Multiple Sclerosis." *New England Journal of Medicine* 365, no. 14 (2011): 1293–1303.
- Confavreux, Christian, Paul O'Connor, Giancarlo Comi, Mark S Freedman, Aaron E Miller, Tomas P Olsson, Jerry S Wolinsky, et al. "Oral Teriflunomide for Patients with Relapsing Multiple Sclerosis (TOWER): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial." *The Lancet Neurology* 13, no. 3 (March 2014): 247–56.
- Gold, Ralf, Ludwig Kappos, Douglas L. Arnold, Amit Bar-Or, Gavin Giovannoni, Krzysztof Selmaj, Carlo Tornatore, et al. "Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis." *New England Journal of Medicine* 367, no. 12 (2012): 1098–1107.
- Fox, Robert J., David H. Miller, J. Theodore Phillips, Michael Hutchinson, Eva Havrdova, Mariko Kita, Minhua Yang, et al. "Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis." *New England Journal of Medicine* 367, no. 12 (2012): 1087–97.
- Cada, Dennis J., Terri L. Leven, and Danial E. Baker. "Dimethyl Fumarate." *Hospital Pharmacy* 48, no. 8 (September 2013): 668–79.
- Freedman, Mark S. "Present and Emerging Therapies for Multiple Sclerosis." *Continuum (Minneapolis, Minn.)* 19, no. 4 Multiple Sclerosis (August 2013): 968–91.
- Cohen, Jeffrey A, Alasdair J Coles, Douglas L Arnold, Christian Confavreux, Edward J Fox, Hans-Peter Hartung,

Eva Havrdova, et al. "Alemtuzumab versus Interferon Beta 1a as First-Line Treatment for Patients with Relapsing-Remitting Multiple Sclerosis: A Randomised Controlled Phase 3 Trial." The Lancet 380, no. 9856 (November 2012): 1819–28.

28. Coles, Alasdair J, Cary L Twyman, Douglas L Arnold, Jeffrey A Cohen, Christian Confavreux, Edward J Fox, Hans-Peter Hartung, et al. "Alemtuzumab for Patients with Relapsing Multiple Sclerosis after Disease-Modifying Therapy: A Randomised Controlled Phase 3 Trial." The Lancet 380, no. 9856 (November 2012).

29. "Alemtuzumab Advisory Committee Briefing Document" <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM374188.pdf>

Peripheral and Central Nervous System Drugs Advisory Committee. November 2013.



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INFECTIOUS DISEASES IN AN INCREASINGLY GLOBALIZED WORLD: HOW IS THE REINSURANCE INDUSTRY MANAGING ITS RISKS?

By Kamran Khan M.D., M.P.H., FRCPC

The Globalization of Infectious Diseases

In 1999, a virus foreign to North America by the name of West Nile arrived in New York City and then spread across the continent. Four years later, a previously unknown virus of bats, now infamously known as "SARS", infected humans in China and then spread to more than two dozen countries, killing 10% of the eight thousand people worldwide that became infected. In 2009, a pandemic strain of the influenza virus known as "H1N1" emerged in Mexico, and then spread to every country in the world in just six weeks. And in the past year, a virus called chikungunya, normally found in Africa and Asia, hit the island of St. Martin, after which it rapidly spread across the Caribbean, and now threatens areas of the continental United States. Today, the largest outbreak of Ebola ever recorded continues to spread widely within three West African countries, recently reaching the large urban centers of Conakry, Freetown and Monrovia.

So why are all these outbreaks happening? Is there just more news of infectious disease outbreaks today, or are they actually increasing in frequency? Confronting these questions requires a look at factors that drive the emergence and international spread of infectious diseases.

Today, a number of global phenomena, from human population growth, to climate change, to surging international air travel, are converging. Foremost, the world's population is expanding at a rapid pace. With over seven billion people in the world today – half of whom live in densely populated cities – there are simply more opportunities for humans to become infected with dangerous microbes. Consequent to population growth is the growing demand for food. Unfortunately, about three-quarters of all new infectious diseases observed in humans have their origins in animals – from SARS, to "bird" flu and even HIV. People tend to become infected with animal pathogens during the production or consumption of livestock or as wildlife ecosystems are disrupted. Furthermore, humans can acquire drug-resistant variants of animal microbes when livestock are fed antibiotics.

While climate change is known to the insurance industry for its impact on the property and casualty market, it sometimes may not be considered in terms of its effect on infectious diseases. Yet many insects from ticks to mosquitoes that can transmit infectious diseases like Lyme or dengue are increasingly able to survive and thrive in areas of the world where the climate is now suitable. In addition to

outbreaks resulting from naturally occurring phenomena, the potential exists for microbes manufactured in laboratories to accidentally escape, or more nefariously, for groups to deliberately release biological agents (e.g., as occurred when weaponized anthrax was dispersed via the U.S. postal system in 2001). And with more than three billion trips on commercial flights worldwide every year, humans are increasingly becoming vectors for the spread of infectious diseases by inadvertently transporting dangerous microbes from one region of the globe to another.

The current outbreak of Ebola in West Africa is now larger than all other outbreaks of the disease combined, with more than 2500 reported cases and nearly 1500 deaths. First discovered in Zaire (now Democratic Republic of Congo) and Sudan in 1976, there is currently no vaccine or treatment known to be effective or safe, despite a mortality rate that can be as high as 90%. What makes the current epidemic unique is that while cases of Ebola are typically only found in remote areas, in this epidemic, cases have emerged in large metropolitan centers. This July, an individual infected with Ebola traveled by air from Monrovia, Liberia to Lagos, Nigeria where a cluster of new cases has since emerged among his healthcare providers. These cases and their contacts are being monitored closely with the hopes of preventing further spread in Nigeria. Two U.S. citizens infected with Ebola, who were working in the region, have been repatriated to the U.S. for medical care. Although this has caused some anxiety in the general population, it is important to note that Ebola virus is spread only when uninfected persons come into contact with the body fluids of infected persons. In an industrialized country like the United States, where the risks of new imported cases of Ebola are generally low but not zero, this largely translates into possible exposures to frontline healthcare providers. Since medical and public health systems and hospital infection control practices in the U.S. are highly robust, the probability of Ebola virus having an impact among the general population is exceedingly low. For insurers with critical illness or life exposure in industrialized areas of the world, this knowledge should be balanced against the widespread reporting of Ebola by the global media, to avoid inflated perceptions of risk.

The Recent Threat of Middle East Respiratory Syndrome (MERS)

Caused by a previously unknown coronavirus, MERS was first identified in the Arabian Peninsula back in 2012. Thought to have made the leap to humans from camels, there remains uncertainty as to just how this virus is actually infecting humans. Once humans are infected however, they are able to transmit

it from person to person. Fortunately, this virus is far less contagious than its 'cousin' of a decade ago, SARS. Largely confined to Saudi Arabia and neighbouring countries, this outbreak has simmered over the past two years. But in the spring of 2014, transmission of this deadly virus – which kills about one third of those infected – increased sharply. While many new infections were related to viral spread within hospitals, the cause of other new infections were unexplained and thought possibly due to contact with camels or unrecognized contaminated areas in the environment. Following this surge in cases came the accelerated international spread of MERS to countries in Western Europe, North Africa, the Middle East, East Asia and even North America (two cases were imported into the U.S.).

What has been challenging with MERS is that there is an incomplete understanding of how it infects humans and, consequently, how best to prevent new infections. Furthermore, it has a broad spectrum of illness, with many of those infected displaying no symptoms at all (incidentally identified when investigating contacts of known MERS cases), others having mild respiratory illnesses that resemble those of common respiratory viruses and, at the other end of the spectrum, severe, life-threatening, respiratory failure. While rapid diagnostic tests have been developed to identify the virus in respiratory specimens along with blood tests that can detect evidence of recent infection, not all countries have robust medical and public health systems that can readily detect MERS. Like SARS, what is especially concerning is that there is no vaccine or effective treatment protocol available (other than supportive management for those who require intensive care).

While many viruses possess the ability to rapidly evolve and take on new characteristics (e.g., become more contagious), fortunately, MERS remains quite limited in its ability to spread from person to person; however, public health officials around the world are also mindful that Saudi Arabia hosts the largest annual mass gathering in the world. Saudi Arabia, custodian of major religious sites in the Muslim world – the cities of Mecca and Medina – sees about three million pilgrims arrive annually from virtually every country in the world. While international pilgrims arrive throughout the year to perform a 'lesser pilgrimage' known as *Umrah*, numbers increase significantly during the holy month of Ramadan. In October 2014, pilgrims will congregate to perform the *Hajj*, a mandatory ritual for all physically and financially able Muslims to perform at least once in their lifetime. Given that this congregation involves massive crowds, pilgrims could potentially become infected with MERS in Saudi Arabia, and then develop illness after they return to their home countries.

While the recent surge in MERS activity across Saudi Arabia has momentarily subsided, public health officials around the globe, including the World Health Organization, will be closely monitoring the situation leading up to, during, and after the *Hajj*.

The Power of Predictive Analytics

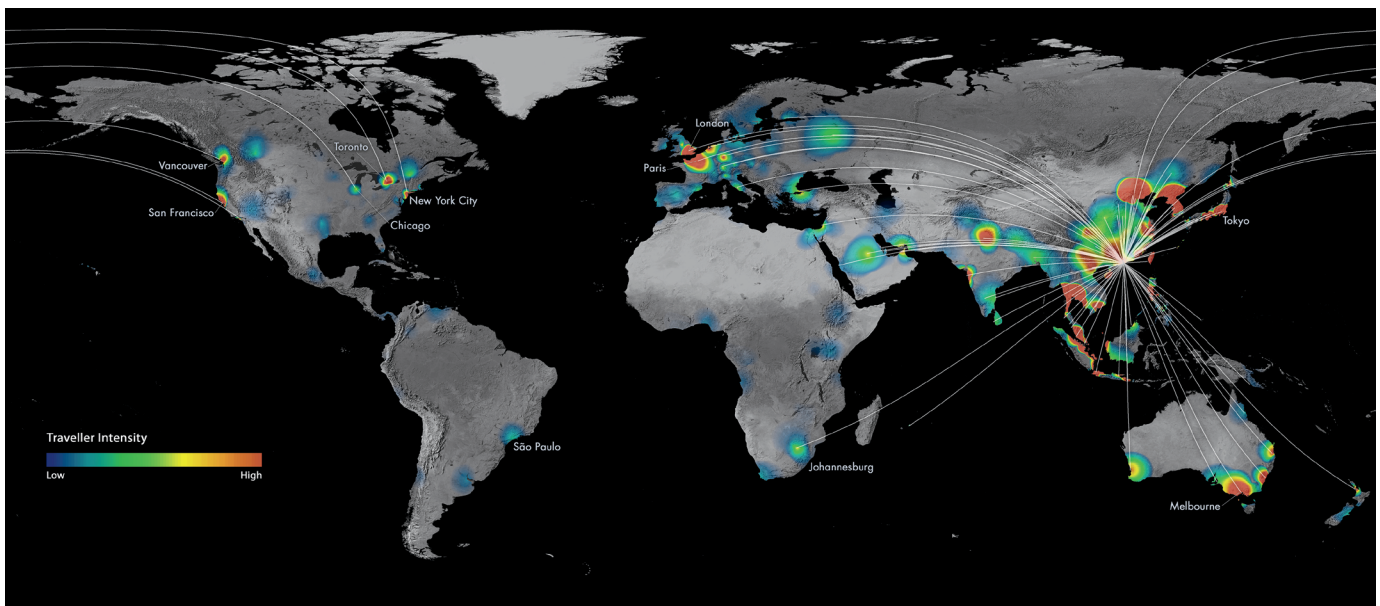
When infectious disease outbreaks with significant potential health risks arise, how does the insurance industry evaluate them? Is a systematic approach adopted that distinguishes a subjective and potentially emotional driven response from an evidence-based, objective assessment of their expected impacts?

As an infectious disease clinician and scientist at an academic teaching hospital, my perspectives on emerging infectious diseases stem from personal experiences that lie outside of the insurance industry. In 2003, after completing my clinical infectious disease and public health training in New York City, I returned to my home town of Toronto just before SARS made its way to Canada from Hong Kong. It was an eye-opening experience that demonstrated just how interconnected and interdependent our world is when it comes to the threat of infectious diseases. It was also an experience that revealed a major gap in our ability to make informed, time-sensitive

help governments better prepare for and respond to the next big infectious disease threat facing their citizens. After years of building a robust research program and integrating it with the technological know-how to produce timely, scientifically validated predictive analytics, my colleagues and I in academia were well prepared for the H1N1 influenza pandemic of 2009. When we accurately predicted the global wavefront of this pandemic based on analytics of worldwide air traffic patterns (publishing these findings in the *New England Journal of Medicine*), it became clear that there was a strong interest in anticipating the impacts of globally emerging infectious diseases from both the public and private sectors alike. Maintaining a strong desire for social impact, my colleagues and I founded BioDiaspora – a social benefit corporation – with a mission to prevent or mitigate the health and economic consequences of future infectious disease threats. During the past five years, we have been partnering with key public health organizations in the world like the U.S. Centers for Disease Control and Prevention and the World Health Organization.

An Outsider's View on the Industry

After meeting a variety of insurance industry stakeholders, it did not take long to realize that, when contemplating infectious diseases, a significant amount of time and energy is spent



Infectious Disease Risk Map

decisions about infectious disease threats arising on the other side of the world. Responding to this unmet need, my colleagues and I began integrating our collective expertise in clinical infectious diseases, population and public health, big data, geographic information systems, predictive modeling and web-technology, to develop innovative tools that could

reflecting upon one historical event – the Spanish influenza pandemic of 1918. Even though it occurred almost a century ago – prior to the advent of antibiotics, intensive care units and other modern medical innovations that help keep people alive – it symbolizes a disconcerting and unexpected spike in morbidity and mortality that could have devastating implications

to the health of populations worldwide. Thankfully, almost a century later, no other epidemics or pandemics have rivaled the estimated 50-100 million deaths that occurred globally as a result of the Spanish flu; but the memory of this event continues to beg the question, could history repeat itself?

From a biological perspective, it is entirely plausible that a pathogen, comparable in its virulence to the 1918 Spanish influenza virus, could emerge. On the other hand, one could argue that modern antibiotics, vaccines, and life-saving critical care technologies that were not available a century ago, would prevent the sheer volume of lives lost in 1918. But a pragmatist might also remind us that there are limits to supplies of antimicrobials and essential medicines, that significant delays still exist when producing vaccines even for the most common of pathogens such as influenza, and that the finite number of intensive care unit beds cannot easily be increased to respond to a sudden unexpected surge in demand.

With enduring memory of the Spanish flu, it is perhaps not surprising that the insurance industry focuses much of its attention on influenza, a highly unpredictable virus that clearly deserves respect. However, it appears that pandemic influenza has become synonymous with the potential for large-scale morbidity and mortality. But in this subtle assumption lies a possible risk – could a high-impact event arise from pathogens other than influenza? Considering the accelerated emergence of so many previously unknown infectious diseases during the past few decades – many making the leap from animals to humans – it is possible that one of these could be the next “big one”. It is also possible that the world might experience more-frequent epidemics in the future, each with smaller impacts than a pandemic, but with cumulative effects on health that could be substantial (epidemics are considered geographically defined events, whereas pandemics are by definition epidemics that spread across the entire world). Considering that present-day scientific knowledge – and future knowledge presumably for some time – is insufficient to anticipate where or when the next influenza pandemic will emerge, just how contagious and deadly it will be, and how well our modern medical and public health systems will be able to respond to it, an important question to ask is just how much energy should be consumed planning specifically for an influenza pandemic?

Infectious Diseases Are Many Things

The term infectious diseases may imply a homogeneous group of illnesses, but in reality they represent a diverse collection of microbes, each with their own unique characteristics, life cycles, and effects on human health. So rather than start with a pathogen – like influenza for example – when evaluating risks to

an insurer, perhaps it makes more sense to start with the type of insurance product being considered. For instance, some pathogens can cause chronic morbidity, which could be of interest to those with substantial disability exposure, whereas others are virulent and could pose risks from a critical illness or life perspective.

A geographically tailored method of evaluating risks to an insurer would be to relate its global exposure to a specific insurance product (i.e., life, disability, critical illness) with the global geographic footprints of infectious diseases relevant to that product, while taking into consideration global travel patterns from those infectious disease footprints. Moreover, understanding local context is critical. The observed health impact from an infectious disease is not just a function of the pathogen itself, but also the susceptibility and vulnerability of the population to that pathogen, as well as the suitability of the environment to facilitate pathogen activity. For example, when cholera was introduced into Haiti in 2010 after a devastating earthquake, access to clean water and enhanced sanitation was disrupted, and consequently hundreds of thousands of infections and thousands of deaths ensued. By contrast, if cholera were introduced into a city in the United States where access to clean water and enhanced sanitation was universal, the microbe would quickly be halted in its tracks. So one can see how a single pathogen could have two very different outcomes when context is taken into consideration. Although more complex than focusing on a single pathogen, tailored risk models could be developed that integrate knowledge of worldwide infectious disease activity, global patterns of travel, local population vulnerability and environmental suitability to infectious diseases, as well as an insurer's geographic exposure by type of insurance product.

Enabling Smarter Decisions

Imagining how big data and predictive analytics could inform smarter decision-making on infectious disease risks facing the insurance industry, it appears that there are opportunities across three time horizons. First, from a long-term perspective (months to years into the future), an insurer could benefit from risk modeling that holistically considers impacts from all relevant infectious diseases in relation to an insurer's existing (or future anticipated) global insurance exposure (as discussed above). Since global leaders in public health use similar approaches to anticipate future epidemic risks, these methods could be adapted and re-purposed to meet insurance industry needs.

On a nearer-term basis (weeks to months into the future), industry stakeholders could benefit from early warnings of key infectious disease events emerging in the world. As the Internet evolves, it is increasingly used as a crowdsourcing medium for

global epidemic intelligence. Since these signals are timely and often precede reporting from official government sources, they can offer valuable insights into potential near-term risks. For example, at the onset of the 2009 H1N1 influenza pandemic, a deviation from the usual seasonal pattern of flu-like-illnesses in Mexico signaled that a possible threat was emerging several weeks before a pandemic risk was formally declared. Although insurers may be limited in their ability to mitigate risks from policies they already hold, timely infectious disease intelligence, coupled with tailored risk assessments, could help inform imminent decisions about new business ventures and opportunities.

Finally, all companies should have robust business resiliency and continuity plans to help them 'ride the wave' of an emergency as successfully as possible, whether related or unrelated to infectious diseases. During the midst of a major global infectious disease event, the health and welfare of human resources may be threatened, supply chains might be disrupted (given today's global nature of business), and decisions about holding capital may arise if an increase in claims is anticipated. Similar to how government health agencies operate, frequent risk assessments based on the most current global information available could help inform short-term decisions (days to weeks into the future) during the midst of an epidemic or pandemic emergency.

Maintaining Perspective

Infectious diseases currently account for about 4% of all deaths in the United States. Although there are far more significant causes of morbidity and mortality across the industrialized world, from vascular disease to cancer and obesity, newly emerging and re-emerging infectious diseases could have significant impacts on the health of populations worldwide over the next few decades. Given that risk assessments in the insurance industry are largely derived from historic data, it is not surprising that there is some discomfort when projecting future risks for major infectious disease events like pandemics, since there are few data points with which to work. This is further complicated by the fact that modern global forces that drive disease emergence and spread are countered by parallel advancements in health technologies that might prevent or mitigate impacts.

Since the recent past might not be predictive of the future when it comes to infectious diseases, the insurance industry may wish to keep key historic events – like the Spanish flu of 1918 – in perspective. Like a brief glance in the rear view mirror, this retrospective look back should not consume an excessive amount of time and energy, since the degree of precision and

the answers sought after may simply not be attainable. But adopting a consistent evidence-based approach to evaluating infectious disease risks going forward, that makes creative use of leading-edge science and technology, could help prevent costly inefficiencies that stem from either over-reaction or under-reaction to emerging threats.

Since SARS brought chaos to cities around the world a decade ago, tremendous scientific and technological advances have been made in preparing for the next major infectious disease event. Government health agencies, often in partnership with academia and the private sector, have taken advantage of advances in big data, predictive analytics, web-technology, and data visualization to anticipate the health and economic impacts of future threats. Because the insurance industry also counts lives and impacts to health, there are important opportunities for it to creatively adapt leading innovations to better plan for, become aware of, and effectively and efficiently respond to inevitable infectious disease threats of tomorrow. ■



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Sudden cardiac death (SCD) is the most common cause of death in Western countries.¹¹

The incidence of sudden death in the general population in Europe is 1.34:100,000 for the ages 7 - 64, with 5 - 8% of those showing no evidence of any structural cardiac abnormality or evidence of any coronary disease at autopsy.^{1,2}

Unexpected sudden cardiac death may occur at any age and results from the development of a malignant aberrant rhythm – ventricular tachycardia (VT) or ventricular fibrillation (VF) – occurring either on a background of structural heart disease, including coronary artery disease, or in a heart that at autopsy is deemed to be structurally normal.

Sudden cardiac death may be aborted if an arrhythmia is very brief and self-terminating but death may otherwise be inevitable in the absence of emergency resuscitation. Sudden cardiac death underlies about 20% of total mortality and 50% of cardiovascular mortality in Western countries. It is the most frequent mode of death during exercise, with 75% of deaths during exercise being cardiac-related.

Heart disease is the most common cause of sudden death in young athletes where physiological demands, coupled with an occult cardiac condition, poses an inherent mortality risk which is greater than in age-matched sedentary individuals.

Coronary artery disease and non-coronary structural heart disease are the most common causes of sudden cardiac arrest. Those structural conditions responsible for sudden arrhythmic death include myocardial infarction and ischemia, valvular heart disease, congenital heart disease and cardiomyopathy.

Ischemic heart disease is the most common structural heart condition responsible for sudden cardiac death in older age groups, while in young people aged <35 heritable hypertrophic cardiomyopathy and other congenital / heritable structural cardiac abnormalities predominate.

Cardiomyopathy may be congenital / heritable or acquired and includes hypertrophic cardiomyopathy, ischemic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and dilated cardiomyopathy.

Inborn errors thus have the most impact on SCD in the young while acquired factors dominate risk in older subjects.

Causes of sudden cardiac death		
Cause	%	Examples of conditions in mortality sublets
coronary artery disease	75-80%	myocardial infarction ischemia-induced arrhythmia ischemic-cardiomyopathy
structural non-ischemic heart disease	10-15%	valvular heart disease congenital heart disease cardiac infiltrative disease cardiomyopathy myocarditis
no structural heart disease	5-10%	primary arrhythmic conditions
acute mechanical conditions	5%	aortic rupture ventricular rupture

This review focusses on sudden cardiac death in those with structurally normal hearts where sudden death occurs in the absence of any overt heart disease at a comprehensive post mortem.

No structural abnormality is detectable in perhaps 5 - 10% of sudden cardiac deaths and these deaths are deemed to be arrhythmogenic. Sudden arrhythmic death is believed to be responsible for approximately 14% of sudden cardiac deaths in young people in the U.K.

These primary lethal rhythm disturbances most commonly result from the presence of an inherited congenital arrhythmogenic disease. These conditions usually have a diagnostic signature on the surface electrocardiogram.

As a group, these conditions are deemed channelopathies, given that they arise as a consequence of abnormalities in the ion channels (sodium, potassium or calcium transport channels) that are responsible for electrical conduction in the heart.

In the past couple of decades a growing number of distinct and potentially lethal heritable channelopathies have been described and include:

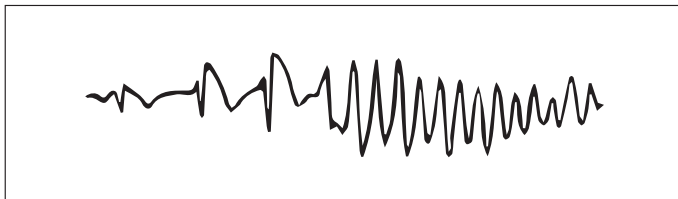
- Long QT syndrome (LQTS)
- Short QT syndrome (SQTS)
- Brugada syndrome (BrS)
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

The genetics of these syndromes are complex. The currently known genetic abnormalities associated with the channelopathies are not detected in all those who have been resuscitated from sudden death or in the deceased who have been submitted to a genetic autopsy.

The Brugada syndrome is probably the most well-known channelopathy, having been described as a clinical entity by the brothers Drs. Pedro, Josep and Ramon Brugada in 1992 as a result of the classical ECG abnormality (previously considered a normal variant) being linked to recurrent syncope in a three-year-old Polish boy whose sister had died suddenly at two years of age. It has attracted a great deal of interest as a risk factor for sudden death because of its high incidence in some parts of the world.

While the Brugada syndrome is a congenital abnormality, the symptoms, including sudden death during sleep, can develop for the first time at any age from infancy to old age, with the mean age of onset of symptomatic electrical events being age 40 ± 22 .⁵

Symptomatic events with syncope or resuscitated cardiac death relate to the abrupt onset of polymorphic ventricular tachycardia or ventricular fibrillation without any prodrome. Brugada is also associated with high rates of paroxysmal atrial fibrillation and other supraventricular arrhythmias with prevalence rates of about 20%.^{3,5}



Brugada type 1 ECG with spontaneous development of lethal ventricular fibrillation

The Brugada syndrome is believed to be responsible for 4 - 12% of all unexplained sudden death and 20% of sudden death in those with structurally normal hearts at autopsy in some series.^{9,4}

The Brugada syndrome, defined as symptoms in an individual with a Brugada ECG pattern, has a prevalence of 1-5:10,000 worldwide and a prevalence of ≥ 5 :10,000 in Southeast Asia.⁵

In Southeast Asia, the Brugada syndrome is the leading cause of death in males under 40 years of age.

The Asian prevalence of a Brugada ECG pattern may be as high as 2% in some areas compared to a European prevalence of 0% - 0.8% and a U.S. prevalence of 0.02%.

Prevalence rates are highest in Thailand and the Philippines.^{1,5}

Brugada is a single gene disease inherited in an autosomal dominant fashion and 20 - 50% will have a family history of sudden death. Up to 60% of Brugada may be sporadic, with no evidence of the disease in a parent or in other relatives, although not all with Brugada will have expressed the phenotype. Some people with a Brugada ECG will remain asymptomatic throughout their lifetimes.⁴

The expression of the arrhythmic phenotype in those with a Brugada ECG may be modulated by the presence of environmental factors, which include fever and certain medications. Genetic factors may also play a role in the promotion of arrhythmias in those with a Brugada ECG pattern.

Although the inheritance is autosomal dominant there is a marked male predominance of the arrhythmic phenotype with a male to female ratio of approximately 8:1. It is not clear why the phenotype is more penetrant in males with a Brugada ECG than in females.

The diagnostic criteria for the Brugada syndrome require two components:

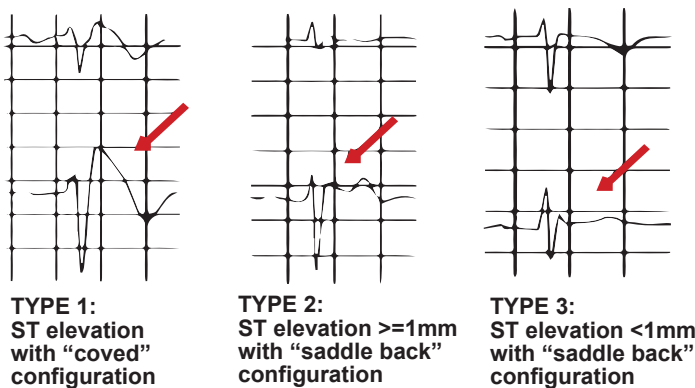
1. Detection of the characteristic ECG pattern plus
2. Clinical characteristics

Three Brugada patterns on the ECG are described (types I, II and III) but a Brugada syndrome is only definitively diagnosed when a type I coved shaped ST segment pattern is identified in the context of one of the following associated characteristics.¹⁰

- Syncope or resuscitated sudden cardiac death
- Nocturnal agonal respiration
- Documented VT or VF
- A family history of sudden cardiac death aged <45
- Type I ECGs in family members
- Inducible VT at electrophysiological study

The type I pattern may be dynamic, temporally variable or concealed making the true prevalence of Brugada syndrome difficult to estimate. The ECG pattern can vary spontaneously and may even disappear periodically.¹² The type I diagnostic pattern may occur spontaneously or be unmasked by a drug challenge in the laboratory. A type I pattern may also be unmasked by fever, metabolic conditions, oral medications and anesthetic drugs.

ECG type II (a saddleback ST segment configuration with ≥ 1 mm ST elevation) and type III (a saddleback ST segment configuration with <1 mm ST elevation) are the most prevalent Brugada ECG patterns in all populations and should not be considered *diagnostic* of the Brugada syndrome. The type I pattern is far less frequent.



A drug challenge in the laboratory is usually mandated in any person with a type II or type III ECG in the context of symptoms or other high risk features, with the intent being to determine whether or not a change in the ECG morphology to a type I can be induced.

A diagnosis of Brugada syndrome can be made when a type II or type III ECG pattern is present in baseline conditions and where there is a conversion to the diagnostic type I ECG after drug provocation provided that one of the non-ECG components of the syndrome is present.³

First-line therapy for people with a Brugada syndrome involves the deployment of an implantable defibrillator (ICD) although there are drugs that have the capacity to suppress ventricular arrhythmias. Several studies have demonstrated the vast superiority of device therapy over antiarrhythmic medications in this population so that drug therapy is not considered appropriate treatment.

Defibrillator deployment is mandated in individuals with aborted sudden death or syncope of cardiac origin in the context of a spontaneous type I pattern.

Strong indications for device deployment also include:

1. Aborted sudden death or syncope in an individual with an inducible type I pattern
2. Inducible VT / VF in an asymptomatic individual with a spontaneous type I pattern

From an insurance perspective, the mortality expectations of Brugada syndrome may preclude an offer, even in the context of device therapy. Despite the protective effects of defibrillators, it is important to realize that ICDs have significant complication rates particularly when balanced against the low annual rates of arrhythmic events even when ICDs have been deployed in persons with symptoms.

The deployment of ICDs for type I ECG patterns in populations with resuscitated sudden death, syncope or positive electrophysiological studies has been associated with device-related complication rates as high as 8.9% per annum. This contrasts with annual arrhythmic event rates of only 2.6% per annum (1.5% in asymptomatic people).¹³

Device complications include inappropriate shocks (with inappropriate shocks being 2.5 times more frequent than appropriate ones), venous thrombosis and pulmonary embolism, pericardial effusions, lead failure, device re-implantation and severe psychological difficulties.¹³

There has been a large focus on the issue of risk stratification in patients at risk of sudden death, although those with aborted sudden cardiac arrest are clearly at the highest end of the risk spectrum and require the protection of a defibrillator.

Stratification in the context of a Brugada ECG in an asymptomatic individual with no adverse family history is very difficult.

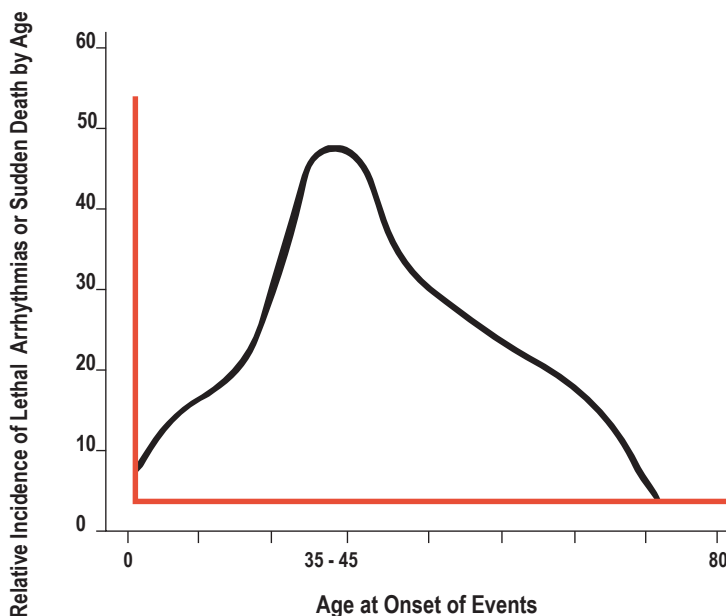
There is considerable disparity in the data regarding the incidence of life threatening-events in individuals with Brugada ECG criteria. The initial studies by Brugada in 1998 reported annual rates of first events of 10% but this study almost certainly included only higher risk individuals. The same authors in 2002 reported annual first event rates of 3.5%.

In 2005, Brugada reported first VF event rates of 1.7% annually. Priori et al. in 2002 reported cumulative cardiac arrest rates by age 40 of 14% in asymptomatic individuals, corresponding to an annual incidence of 0.35%. That same group in 2005 reported annual rates of 1%.

Eckardt 2005 reported a first event in 0.8% of individuals with type I Brugada ECGs followed over a 40 ± 50 month period corresponding to an annual event rate of 0.24%, much lower than in other studies.⁸

The reasons behind the apparent progressive decline in annual event rates over time is not clear but probably results from the inclusion of lower risk phenotypes in some studies and the inclusion of type II and type III in the Priori data.^{5,6,7}

In the most recent review of the international Brugada registry the lifetime risk of sudden death or ventricular fibrillation is reported to be 25% (mean age 42 ± 15), with most individuals remaining asymptomatic. Reports from other series describe lifetime rates of syncope or sudden death in 17-42% of diagnosed individuals.



Previous syncope has been reported in up to 23% of those with cardiac arrest.¹⁶

Event rates are higher in Asian populations with Brugada ECGs than in European populations suggesting differing genetic predispositions.

Psychotropics, anesthetics, antihistamines, cocaine and other drugs are well-documented precipitants of the type I pattern and may induce symptoms. Medications thus increase the risk of penetration of the syndrome in an otherwise asymptomatic person regardless of the ECG morphology.²

The lack of symptoms at older ages in an applicant does not protect against sudden death or arrhythmogenic syncope.

Asymptomatic individuals with no symptoms and a negative family history are not necessarily at low risk.¹¹ Those with a spontaneous type I pattern are at a higher risk than those where a type I morphology has only been exposed by a drug challenge.^{2,14}

Individuals with a type I ECG and symptoms have a RR = 6 of death compared to those with a type I ECG and no symptoms. There is no good evidence that a lack of a family history is sufficiently protective: asymptomatic individuals with a characteristic ECG and no family history are not necessarily at low risk.

The serendipitous finding of a spontaneous type I Brugada ECG in an applicant might lead to a decline, although the literature suggests a high negative predictive value (93%) for events in asymptomatic people if arrhythmias are not inducible at an electrophysiological study.^{1,15}

The annual event rates in asymptomatic people with a type I pattern reported by Obeyesekere in 2011 was approximately 0.5% compared with annual event rates of 7.7% in those with aborted SCD.²

Brugada reported recurrence rates of about 20% in aborted SCD in type I ECG.⁹

Approximately one third of asymptomatic type I individuals will have inducible VT /VF at an electrophysiological study but there is conflict in the data as to whether inducibility predicts the risk of spontaneous VT/VF. From an insurance perspective a negative VT/VF provocation study in a type I morphology does not mitigate risk despite the negative predictive value.

The chance finding of a type II or type III pattern in an asymptomatic applicant may allow terms if there have been no symptoms and particularly if there is no adverse family history. In completely asymptomatic individuals with only drug inducible type I patterns the event rates are low.¹ Clinical practice guidelines do not mandate drug provocation testing in non-type I patterns in people with no symptoms as this does not appear to add value to risk stratification. There is nonetheless a view that this approach is useful in terms of providing advice on lifestyle, fever management, medication use and the management of syncope.

The Brugada ECG signature and the ECG signatures of other occult syndromes that have the potential to induce malignant arrhythmias have important mortality implications. This supports the utility of the ECG at underwriting, particularly in Southeast Asian and other high-risk populations. ■

References

1. Mizusawa Yuka Circ Arrhythm Electrophysiol 2012;5:606-616
2. Obeyesekere MN Circ Arrhythm Electrophysiol 2011;4:958-964
3. Letsas KP Journal of Cardiovascular Medicine 2007;8:803-806
4. Campouzano O Curr Opin Cardiol 252010;25:210-215
5. Antzelevitch C Pace 2006;29:1130-1159
6. Priori SG Circulation 2002;105:1342-1347
7. Priori SG Circulation 2005;112:285-291
8. Eckardt L Circulation 2005;111:257-263
9. Brugada P JACC 2003 Vol 41 (10)
10. Fowler SJ Curr Opin Cardiol 2008;24:74-81
11. Cerrone M European Heart Journal 2011;32:2109-2120
12. Hoogendijk MG Circ Arrhythm Electrophysiol 2010;3:283-290
13. Sacher F Circulation 2006;114:2317-2324
14. MacKenzie R J Insurance Medicine 2001;33:106-109
15. Anderson JL JACC 2013;61
16. Begona B Progress in Cardiovascular Diseases 2008;51(1)1-22



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INTRODUCTION TO SNOMED-CT

By Jeff Heaton

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Are you feeling a bit snowed under by the plethora of codes being promoted for healthcare? Many healthcare and regulatory groups are endorsing SNOMED-CT as a replacement for most of them. The EHR Initiatives team at RGA is using SNOMED to help better understand the relationships between codes. SNOMED-CT provides relational information to help classify codes beyond the hierarchical information provided by other coding systems.

Systematized Nomenclature of Medicine for Clinical Terms (SNOMED-CT) is the current version of the SNOMED standard that is controlled by the International Health Terminology Standards Development Organization (IHTSDO). All SNOMED versions prior to SNOMED-CT are scheduled to expire in 2017. SNOMED CT is an Electronic Medical Record (EMR) coding standard that includes clinical findings, symptoms, diagnoses, procedures, body structures, organisms and other etiologies, substances, pharmaceuticals, devices and specimens. SNOMED-CT is one of the most comprehensive multilingual EMR coding standards.

Because SNOMED-CT is very comprehensive, it overlaps many existing EMR coding standards. SNOMED-CT coding provides the same sort of symptom, procedure and diagnosis information as ICD-10-PCS and ICD-10-CM. Additionally, the pharmaceutical and substance aspects of SNOMED-CT provide much of the same information as RxNorm, Generic Product Identifier (GPI) codes, National Drug Code Directory (NDC) codes, Unique Ingredient Identifier (UNII) codes and British National Formulary (BNF) codes. Furthermore, SNOMED overlaps with other coding standards for body structures, organisms, devices and specimens. Interoperability between SNOMED and other coding standards is provided by both free and proprietary General Equivalence Mappings (GEM) and crosswalks.

IHTSDO provides SNOMED data royalty-free to licensees through its website <http://www.ihtsdo.org/snomed-ct/>. Signing up for a license is free and IHTSDO's verification process generally takes several days. Unlike many other public coding standards, SNOMED-CT provides a great deal of direction for the use of its code and data. The SNOMED-CT data files define the table structure and update procedure for the codes. Additionally, the provided

source code provides best practice examples for how to access the SNOMED-CT data. This openness eases technical implementation of the SNOMED standard.

Inside a SNOMED-CT Code

The SNOMED-CT code for the common cold is 82272006. This is not simply an index number, as there is meaning encoded into 82272006. To understand this meaning, it is important to understand exactly what SNOMED-CT seeks to encode. SNOMED-CT encodes four primary concepts:

- Concept codes – numerical codes that identify hierarchical clinical terms
- Descriptions – multilingual descriptions of the concept codes
- Relationships – defines links between concept codes with related meaning
- Reference sets – allows the grouping of related concept codes and descriptions

The code 82272006 is the SNOMED-CT Identifier (SCTID) for the common cold. This is the actual SNOMED-CT code that would be entered into an EMR system. SCTIDs are numeric codes, up to 18 digits long. There are two types of SNOMED-CT code. SCTID short-format codes are the codes provided by IHTSDO. Additionally, long-format SCTID codes allow third-party extension to the SNOMED-CT standard. The actual SCTID values are compound elements with several sub-values concatenated together. The last digit of an SCTID is always a check digit that verifies the validity of a SNOMED-CT code. The check digit is important because SNOMED-CT codes are often hand-entered and can be prone to human error. Figure 1 shows the layout of the SCTID for the common cold (82272006).

As you can see from Figure 1, the short-format code has a partition id and check digit. The two-digit partition-identifier distinguishes the identifiers of different component types and prevents the situation wherein a single identifier cannot be allocated to both a concept and a description. The standard short form also includes an item id that specifies the actual concept or description being coded.

Figure 1: Structure of a SNOMED-CT SCTID



SNOMED-CT Relationships

SNOMED-CT allows relationships to be defined between SCTID codes. There are more than a million standard relationships defined in the 2014 SNOMED-CT standard. There are several types of SNOMED-CT relationships. An “is a” relationship can be used to define what a concept is. For example, according to SNOMED-CT a common cold is a “viral upper respiratory tract infection”. A “viral upper respiratory tract infection” is a “disorder”. Additionally SNOMED-CT concepts can have attributes. For the common cold, attributes define the pathological process, finding site, and causative agent for a common cold. There are many different attributes defined in SNOMED. These attributes are divided into hierarchies. The main SNOMED-CT hierarchies are listed here.

- Clinical finding
- Procedure
- Observable entity
- Body structure
- Organism
- Substance
- Physical object
- Physical force
- Events
- Environmental/geographic location
- Record artifact

The relationship data is used by software in a variety of ways to speed up coding by users. Additionally, this information is very useful for analytics to relate and contrast SNOMED concept entries.

SNOMED Compositional Syntax

SNOMED permits a compositional syntax that allows SCTID codes to combine to provide greater specificity than individual SCTID codes would allow. For example, there is no explicit concept for a “third degree burn of left index finger caused by hot water”. However, using the compositional syntax it can be represented as:

```
284196006 | burn of skin | :  
, 116676008 | associated morphology | = 80247002 | third degree burn injury |  
, 272741003 | laterality | = 7771000 | left |  
, 246075003 | causative agent | = 47448006 | hot water |  
, 363698007 | finding site | = 83738005 | index finger structure
```

This permits the number of core SNOMED codes to be kept relatively tight, and the more-unusual conditions to be coded using compositional syntax.

Let us compare this with another code classification system that does not have a compositional syntax capability. Assume one has a code for a burn on the skin = 1000. If one wishes to indicate the degree of the burn, one must now multiply the one code by at least three to cover three degrees: 1000, 2000, and 3000. This burn could be on the left, right, or both sides, so now we have just multiplied by three again. We have now expanded to nine codes: 1100, 1200, 1300, 2100, 2200, 2300, 3100, 3200, 3300. Let us assume any of ten agents could have caused this burn (acid, flames, sun exposure, hot water, scalding drive-through coffee, etc.). We just multiplied our code set by ten to now have 90 codes now (I will not list them all here). We still have not even described whether this burn is on a finger, toe, which finger or toe, arm, ear, etc. so at least 50 body sites will multiply the code set by 50 to get 4,500 codes now for this burn. It is easy to see that the more specific we get, the more our code set must expand and that each expansion is not an addition but a multiplication of the total number of codes for that impairment. Add timing, area covered, etc., and we easily top a million burn codes.

The SNOMED compositional syntax approach lets one be as specific as one wishes regarding cause, location, severity, etc. without going overboard with codes for weird combinations one may never use.

It also provides a way for third-party entities to extend the code set as needed for almost any unforeseen situation. Up to 10,000,000 external parties can each add up to 100,000,000 special purpose codes as needed! These third-party codes are longer than the standard short-form SNOMED-CT codes. The code 999999990989121104 is an example of such an extension code. To issue extended codes, a coding entity must register a namespace with IHTSDO. This namespace provides a block of codes for the entity to assign.

SNOMED codes are also not restricted to English. Currently, SNOMED-CT is available in U.S. English, U.K. English, Spanish, Danish, and Swedish. More languages are being added and a guide exists for adding one's own favorite language version.

Conclusions

The openness of SNOMED-CT makes it easy to find needed technical information about the standard. This openness extends into the free software and database specifications provided by IHTSDO. All of these ease adoption of the SNOMED standard. Not all standards are this easy to work with.

The SNOMED-CT relationships provide a rich source of data between encoded conditions. This information is very useful for analytics and modeling. The hierarchical definition of codes provides several useful data points to help classify SNOMED concepts to an analytical system. SNOMED-CT is a rich, open, extendable EMR coding standard that is very useful for a variety of insurance applications. ■

References

- Giannangelo, K. (2010). *Healthcare code sets, clinical terminologies, and classification systems*. Chicago, Ill: American Health Information Management Association.
- International Health Terminology Standards Development Organization (IHTSDO). SNOMED CT® *Technical Implementation Guide January 2014 International Release*. Retrieved from: www.snomed.org/tig.pdf
- Trotter, F. & Uhlman, D. (2011). *Hacking Healthcare: Meaningful use and beyond*. Sebastopol, CA: O'Reilly.



Jeff Heaton

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Jeff Heaton recently joined the Electronic Health Records (EHR) Initiatives team at RGA as an EHR Informatics Scientist. In one of his first tasks, he was asked to create a utility to allow an underwriter to enter information on a code-by-code basis. This required mapping the CDC-provided XML files to an Oracle database, while preserving the hierarchical nature of the codes.

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Presenters:

Tim Rozar
Senior Vice President, Global Research and Development
RGA Reinsurance Company

Derek Kueker
Actuary
RGA Reinsurance Company

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Presenters:

Scott Rushing
Vice President and Actuary, Global Research and Development
RGA Reinsurance Company

John Buppert
Vice President of Sales – Insurance
TransUnion

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