Housecalls

Spring 2019

Richard Braun, MD
Vice President & Chief Medical Officer
rbraun@scor.com

INSIDE THIS ISSUE

DETERMINING FUTURE MORTALITY

Examining a Population

Take a step back from the individual cases that you see daily and look at mortality from a population perspective. That is how the SCOR actuaries have asked us to assist them in determining future mortality. Obviously, future mortality is crucial in pricing of life insurance products, annuities and pension liabilities. In order to provide the best information, we embarked on an effort to collaborate with medical experts and get their perspectives on what the future holds in their areas of expertise.

The three most common causes of death in the US are cardiovascular disease, cancer and dementia/neurological, so those were the specialties that we engaged. We had identified a number of "drivers" (trends in behavior, technology, medical advances, etc.) that had likely impacted mortality during the last 15 years or so. Data on mortality trends over the past 15 years was provided to the medical experts so they could compare their knowledge of drivers to effects on mortality.

The medical experts were then asked to project if those drivers were the correct ones and if they would continue to drive changes (both good and bad) into the future. Experts were asked to estimate the amount of change and to suggest any new drivers that might be on the horizon.

As an example, most cardiovascular experts agreed that the reduction in smoking during the past few decades was a major driver of the decrease in cardiovascular deaths. However, reductions in cardiovascular death rates have leveled out more recently. And the question is what will the next major driver be? Will increasing obesity reverse the gains previously made? Will vaping increase and claw back at least a part of the mortality improvements due to smoking cessation?

Continued

SCOR
The Art & Science of Risk

DETERMINING FUTURE MORTALITY

Examining a Population

Continued, page 1

The opinions of the experts were collected through surveys and interviews. These results were then analysed with increased weight given to specialists in the fields examined. Competing causes of death were also considered (e.g., someone surviving a myocardial infarction may then develop cancer). Overall improvements were predicted in mortality from most causes of death. The information was ultimately used by the actuaries to improve their models of insured lives mortality.

Our Spring edition of *SCORviews* will include an article on this and another expert judgement study that SCOR Global Life in the Americas conducted as part of our Global Mortality Improvement initiative.

Also in this issue, the case of Mycobacterium Avium complex (below) which is increasing in incidence around the world. Whether this is due to improved detection or another cause is not known at this time. Dr. Rosace presents a case of postural tachycardia syndrome (page 6). And Dr. Rooney presents a Puzzler on a family history of Hypertrophic Cardiomyopathy (back cover).

CASE #1

Mycobacterium Avium Complex

Richard Braun, MD
Vice President & Chief Medical Officer
rbraun@scor.com

A 65-year-old woman applied for life insurance. She presented to her doctor six months prior to the application. She complained of shortness of breath for the prior two years and a nagging non-productive cough for the past six months. An evaluation by a pulmonologist revealed an SpO2 of 90, a mildly reduced FVC/FEV1 of 69% of predicted, a DLCO of 65% predicted and scattered small nodules and small areas of bronchiectasis bilaterally on computed tomography of the lungs. Bronchial biopsies were benign and washings showed infection with Mycobacterium Avium Complex organisms. No treatment was prescribed. Insurance labs are negative for HIV and within normal limits. Body Mass Index on the exam was 19.

What is the significance of an infection with Mycobacterium Avium Complex and what is the anticipated prognosis?

Mycobacterium infection can be separated into two categories: those causing tuberculosis or leprosy (i.e., Mycobacterium tuberculosis complex) and the Nontuberculous mycobacteria (NTM). NTM organisms can be further divided into rapidly growing and slow growing species (Table 1).

NTM are free living and widely present in the environment. There have been an estimated 200 species of NTM identified.

The Mycobacterium Avium Complex (MAC) is a subset of the NTM and is made up of genetically similar organisms that are generally slower growing. People who are immune compromised (e.g., HIV infected, being treated for cancer, recipients of organ transplants) are at increased risk for NTM infection, but so are older, non-immunocompromised individuals who have some underlying lung disease. One study found NTM isolates in 13% of cystic fibrosis (CF) patients tested at 21 treatment centers across the U.S.

MAC organisms have been identified in the plumbing/water supply of infected individuals, and NTM have been found in peat-rich potting soil.

TABLE 1 - MORE COMMON DISEASE-CAUSING MYCOBACTERIUM

Mycobacterium Tuberculosis	Nontuberculous Mycobacteria	
	Rapidly Growing	Slow growing
M tuberculoisis	M. fortuitum complex	M. avium complex
M. bovis	M. chelonae	M. terrae complex
M. africanum	M. abscessus	M. ulcerans
M. microti	M. smegmatis	M. xenopi
M. canetti	M. mucogenicum	M. malmoense
M. leprae		M simiae
		M. szulgai
		M. kansasii
		M. marinum
		M. gordanae
		M. scrofulaceum

More than 200 species of Mycobacteria have been identified. This chart shows some of the more common disease-causing mycobacterium.

Population studies in the U.S. and Canada indicate that the incidence of NTM lung disease increased in the first decade of the 21st century. Details of the cause (aging of the population, more immunocompromised individuals, more awareness and testing for the infection, etc.) were not apparent from the studies. Skin testing studies for exposure to MAC have found that about 40% of subjects are reactive with a predominance (46%) of southern states over northern states (33%).

Infection with NTM or MAC in immunocompromised individuals is beyond the scope of this case review. However, lung disease associated with MAC occurs in a few typical settings not associated with immune suppression or CF.

Middle-aged or elderly men, often alcoholics or smokers who have underlying lung disease, appear susceptible. In addition, non-smoking women over age 50 who may or may not have underlying lung disease can present with an interstitial pattern on chest X-ray and subsequently test positive for MAC infection. There is also a condition called "hot tub lung" that is a result of hypersensitivity pneumonitis due to MAC. As the name implies, it is associated with hot tub use. Occasionally MAC infections can present as solitary pulmonary nodules.

Diagnosis

The diagnosis of NTM is made in a person with pulmonary symptoms who has fibrosis and cavitations or multifocal bronchiectasis with multiple small nodules on chest radiographic studies, after other causes have been excluded. Additional diagnostic criteria are either two positive sputa obtained at different times, one positive lavage or a lung biopsy positive for NTM.

Treatment

In MAC infections, treatment decisions are often made based on clinical status and radiographic findings. Patients with fibrocavitary disease may have rapid progression with destruction of lung tissue and for that reason are usually started on treatment at the time of presentation.

Patients presenting with nodular bronchiectatic findings on imaging have a more variable course and may be followed closely rather than started on treatment. One series reported that patients with this type of presentation were initially observed without treatment 10%-25% of the time.

Reasons for delaying treatment include the presence of co-morbidities, the prolonged course of treatment (15-18 months) with dropout rates up to 33%, side effects, the development of antimicrobial resistance and ultimate recurrence rates that approach 50%. Studies of the organisms involved in recurrence revealed that ~25% were recurrence, while ~75% were reinfections.

Continued

CASE #1

Mycobacterium Avium Complex

Continued, page 3

Risk factors

Risk factors for progression of MAC include low BMI, increasing number of segments involved, cavitary disease, male sex, older age, hypoalbuminemia, anemia and elevated inflammation markers (ESR, CRP). A series of 265 patients with untreated nodular bronchiectatic MAC were followed for a mean of 32 months, and 48% had progression of disease requiring treatment.

Cavitations and consolidation on computed tomography increased the risk of progression. Another series of 782 patients with nodular bronchiectatic MAC, a mean age of 68.1 years and a median follow-up of 4.3 years had a 10-year mortality rate of 27.4%.

Returning to the case

The applicant was recently discovered to have MAC pulmonary disease. There are poor prognostic signs in mildly impaired pulmonary function, bronchiectasis and low BMI. It would be prudent, given the recent diagnosis, to wait for subsequent follow-up to assess the rate of progression.

REFERENCES

Johnson M. et al. "Nontuberculous mycobacterial pulmonary infections," J Thorac Dis 2014;6(3):210-220.

Marras T, et al. "Variable agreement among experts regarding Mycobacterium avium complex lung disease," Respirology 2015 20(2):348-51.

Gochi M eta l. "Retrospective study of the predictors of mortality and radiographic deterioration in 782 patients with nodular/ bronchiectatic Mycobacterium avium complex lung disease," BMJ Open 2015;5:e008058.

Lee G, et al., "Nodular Bronchiectatic Mycobacterium avium Complex Pulmonary Disease: Natural Course on Serial Computed Tomographic Scans," Ann Am Thorac Soc 2013; 10(4):299-306.

Cowman, S et al., "Latent class analysis to define radiological subgroups in pulmonary nontuberculous mycobacterial disease," BMC Pulm Med 2018;18:145.

UpToDate – Sections "Preview of nontuberculous mycobacterial infections in HIV-negative patients", "Epidemiology of nontuberculous mycobacterial infections", "Diagnosis on nontuberculous mycobacterial infections on the lungs in HIV-negative patients", and "Treatment of Mycobacterium avium complex lung infection in adults" – last accessed 2/28/19.


SCOR
The Art & Science of Risk
Let's face **the unexpected** together
You can confidently manage your high-risk life business with support from SCOR Global Life's experienced and specialized facultative underwriting team. As one of the largest facultative reinsurers in the industry, we understand the particular risks associated with impaired, substandard and high face amount business. Our expert underwriters and medical directors can help you place high-risk business quickly and competitively. You can also count on SCOR Global Life for help in developing underwriting requirements, guidelines and training programs.
For more information, please contact Kristin Ringland at kringland@scor.com.
www.scor.com
© Posteriori / Shutterstock

CASE #2

Postural Tachycardia Syndrome (POTS)

Regina Rosace, MD
Assistant Vice President, Medical Director
rrosace@scor.com

A 28-year-old female applies for life insurance. She states that she had been diagnosed with chronic fatigue syndrome and POTS at the age of 19 years. She has no history of syncope, only presyncope. She has never been involved in an accidental trauma. She currently works with a personal trainer, takes propranolol daily and is mindful to increase her salt and fluid intake. Although she is no longer able to participate in long distance runs and races, she is able to work from home at a desk job and care for her family, which includes a husband and a three-year-old child.

What is a POTS, and what are the mortality implications?

Postural tachycardia syndrome (PoTS or POTS), also known as Postural orthostatic tachycardia syndrome, is a heterogenous clinical syndrome characterized by sustained and excessive sinus tachycardia upon standing without orthostatic hypotension with chronic symptoms (≥6 months) of orthostatic intolerance which are relieved by recumbence.

POTS is a chronic disorder. Many individuals can experience similar symptoms during periods of dehydration or acute illnesses, and those cases are excluded from this definition.

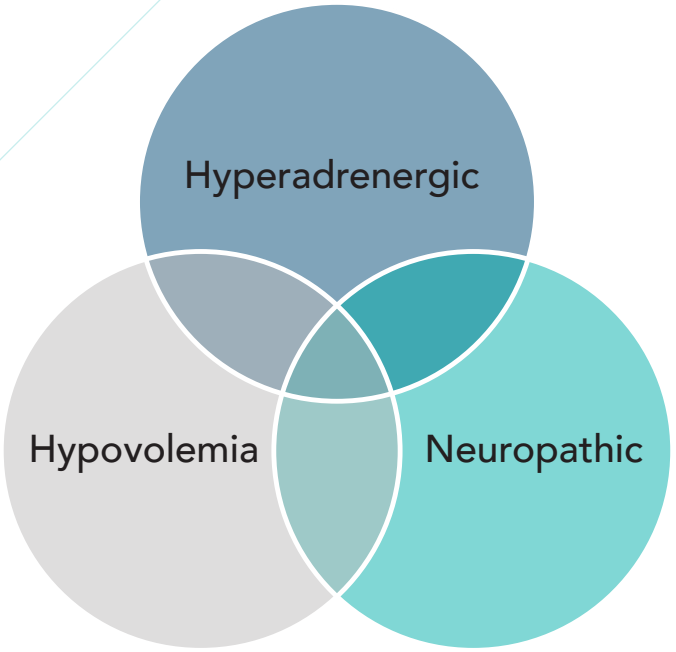
Epidemiology

The prevalence is estimated to be 0.1% – 1% of the US population, and the syndrome has gained significant clinical interest during the past 20 years.

POTS may occur in children as young as six years old and rarely in older adults, but generally ages 13-50 are the most frequently affected with a very strong female predominance (4-5:1).

Family history of orthostatic intolerance is found in approximately 13% of patients.

Polymorphisms in genes coding for nitric oxide synthase and the beta-2 adrenoreceptor have been found in a few patients, and in one family, a genetic mutation in the gene encoding the norepinephrine transporter has been identified. While these findings are not present in most POTS patients, this supports a component of neurosympathetic etiology in at least some patients.



Pathophysiology

POTS is a clinically defined syndrome with a set of symptoms that are the manifestation of diverse underlying processes. While some authors break POTS into subtype labels, there are no standard definitions. As such, a more realistic way of conceptualizing this disorder is evaluating separate components with varying degrees of overlap.

A large portion of POTS patients show evidence of partial sympathetic neuropathy due usually either to a distal small fiber neuropathy and/or cardiac sympathetic denervation.

In addition, a similarly large portion of patients show evidence of a hyperadrenergic state, determined by using measurements of norepinephrine and susceptibility to isoproterenol. Hypovolemia is a very common finding as well, often accompanied by cardiac atrophy.

Acute restoration of intravenous volume tends to attenuate symptoms in many. In some, mast cell activation is noted by the presence of episodic flushing and elevated measurements of methylhistamine in the urine shortly following flushing episodes.

There appears to be an autoimmune component, as evidenced by various cytokine and antibody levels, onset immediately post viral illness and the presence of comorbid autoimmune disease at a higher rate than in the population.

Finally, while frequently present, it remains unclear whether deconditioning represents a primary cause of POTS or a secondary result of the chronic illness. Using the knowledge of the above findings, treatment is tailored to symptomatology.

Diagnostic criteria for POTS

- Heart rate increase ≥30 bpm within 10 minutes of upright posture in adults. Heart rate increase of ≥40 bpm within 10 minutes is required in adolescents age 12–19 years.
- Absence of orthostatic hypotension defined as a sustained drop in blood pressure ≥20/10mmHg within three minutes of upright posture.
- Symptoms of orthostatic intolerance for greater than or equal to six months.
- Absence of overt causes for sinus tachycardia such as acute physiological stimuli, dietary influences, other medical conditions and medications.

Continued

CASE #2

Postural Tachycardia Syndrome (POTS)

Continued, page 7

TABLE 1 — HEART RHYTHM SOCIETY RECOMMENDATIONS FOR EVALUATION OF POTS

Initial evaluation	Additional evaluation if clinically indicated
Medical history	*Blood work* to rule out dehydration, anemia, thyroid disease
Family medical history	*Cardiovascular testing* (ECHO, Holter, exercise stress test) to rule out suspected cardiac condition or structural abnormalities
Physical examination	*Head up tilt table testing* (HUTT) for patients with normal orthostatic vital signs but high clinical suspicion or for those with seizures
Orthostatic vital signs	*Autonomic function tests* for patients with symptoms of autonomic neuropathy or for those who do not markedly improve with treatment
Electrocardiogram	

Source: Sheldon et. al.

Clinical features and diagnosis

Presentation often occurs in teenagers within a few years of their growth spurt and frequently following an identifiable trigger such as an acute illness or injury. The clinical presentation is essentially a prolonged exaggerated heart rate increase in response to an upright postural change, orthostasis, with concomitant symptoms. These symptoms include dizziness, lightheadedness, headache, weakness, blurry vision, palpitations, nausea, fatigue and occasionally syncope.

By definition, the symptoms must resolve with lying down. They can occur insidiously or abruptly after an acute event. These patients may present to emergency rooms, primary care physicians, cardiologists or neurologists.

The minimal requirements needed when evaluating POTS are a medical history, a family history, a physical exam including orthostatic vital signs and a resting EKG.

Clues in the medical history which may support POTS include personal or family history of similar symptoms, evidence of joint hypermobility or autoimmunity. Joint hypermobility and Ehlers Danlos Syndrome are strongly associated with POTS.

A thorough history, physical exam and EKG help rule out some of the differential diagnoses such as vasovagal syncope, an accessory bypass tract or cardiac conduction abnormalities.

Head up tilt table testing (HUTT) is a test commonly described in the literature, where HR and BP are measured continuously while the patient is supine on a tilt table which is moved to various degrees of incline. This eliminates the muscle pump activity normally present in individuals while standing upright, while passively moving the patient into an upright position.

The measurements are thought to evaluate a patient's ability to accommodate to the normal hemodynamic shift while transferring from a supine to an upright position. A few limitations to the HUTT include:

- the physiologic responses activated during HUTT are different than during active standing
- often there is a greatly increased tachycardia generated during HUTT as compared to normal upright orthostatic testing
- controlled studies have not been performed in younger individuals.

Because of these issues, HUTT must be interpreted as part of the entire clinical picture.

Continued

CASE #2

Postural Tachycardia Syndrome (POTS)

Continued, page 9

Comorbidities

Obviously, syncope (rarely) and presyncope (more commonly) are quite debilitating in regards to everyday, independent activities and functioning. Other comorbidities commonly present include: hypermobility syndromes, gastrointestinal abnormalities, chronic fatigue syndrome, fibromyalgia, sleep abnormalities, chronic pain and Raynaud-like symptoms, while less frequently headaches and urinary issues are troublesome. Each patient is evaluated and treated specifically to their particular symptom complex.

Treatment

There is no cure for POTS, but there are many non-pharmacologic and pharmacologic approaches toward relieving the POTS symptoms and improving the quality of life.

Non-pharmacologic approaches are the foundation of management. If they are insufficient, "off label" pharmacologic methods may be tried. The FDA has not approved any medications for pharmacologic treatment.

The treatments are tailored to symptoms in each individual patient. While there is no cure for POTS, generally the symptoms can be controlled and hopefully, the patient returns to his or her previous level of activities.

TABLE 2 — TREATMENT OPTIONS FOR POTS

Non-pharmacological treatments	
Exercise training (reconditioning)	Counteracts cardiac atrophy
Increased salt-fluid intake	Counteracts hypovolemia
Sleeping in head-up position	Increases stroke volume
Compression garments	Counteracts venous pooling in lower body
Physical countermeasure maneuvers	Encourages muscle pumping which improves venous return
Pharmacological treatments	
Blood volume expansion	Salt supplementation, fludrocortisone, desmopressin (DDAVP), IV saline, erythropoietin
Reduction of heart rate test	Propranolol, ivabradine, pyridostigmine
Peripheral vasoconstriction	Midodrine, octreotide, methylphenidate, droxidopa
Sympatholysis	Clonidine, methyldopa

Prognosis

Unless one is in harm's way (e.g., standing on the edge of a cliff), POTS is not lethal, and the mortality rate is thought to be standard. It is a chronic condition with waxing and waning, generally with eventual improvement. The morbidity, however, can be significant in some patients with great interference in normal daily activities and quality of life.

Returning to the Case

This lady has a history of chronic fatigue and POTS. She is well controlled with non-pharmacologic and minimal pharmacologic treatment, with good function. She delivered a child and cares for her family while holding down a job. She was assessed at near normal mortality.

REFERENCES

Arnold, Amy C., Jessica Ng, and Satish R. Raj. "Postural tachycardia syndrome–Diagnosis, physiology, and prognosis." Autonomic Neuroscience: Basic and Clinical (2018).

Fu, Qi, and Benjamin D. Levine. "Exercise and non-pharmacological treatment of POTS." Autonomic Neuroscience: Basic and Clinical 215 (2018): 20-27.

Miller, Amanda J., and Satish R. Raj. "Pharmacotherapy for postural tachycardia syndrome." Autonomic Neuroscience: Basic and Clinical (2018).

Ojha, Ajitesh, Thomas C. Chelimsky, and Gisela Chelimsky. "Comorbidities in pediatric patients with postural orthostatic tachycardia syndrome." The Journal of pediatrics 158.1 (2011): 20-23.

Sheldon, Robert S., et al. "2015 Heart Rhythm Society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope." Heart Rhythm 12.6 (2015): e41-e63.

www.uptodate.com last accessed 2/4/2019

SOLVE

Lab Puzzler...

By Bill Rooney, MD
Vice President,
Medical Director
brooney@scor.com

Here is the latest Lab Puzzler to solve.

A genetics test has been performed, and results are normal. Does that rule out the presence of a specific disease you seek?

A 33-year-old male applies for $750,000 of life insurance. He reports having a strong family history (FH) of cardiac problems. He himself has had no cardiac complaints in the past. He has seen a cardiologist because of the FH. A genetic test for hypertrophic cardiomyopathy was negative, but the cardiologist continues to follow this patient closely. Why?

Visit the *Housecalls* page on our website to find the answer at www.scorgloballifeamericas.com. Click on Spring 2019 Puzzler to confirm your findings.

Family History		
Father	Died age 44	Sudden death
Paternal GF	Died "in his 50s"	Sudden death
Paternal Aunt	Died recently (age ?)	Diagnosed with hypertrophic cardiomyopathy (HCM). HCM discovered after developing atrial fibrillation which was followed by a stroke.

APS Information		
10/2017	Cardiology evaluation	EKG: "nonspecific ST/T wave changes" Echocardiogram: WNL Genetic testing: Negative Plans to follow up in 1 year with echocardiogram
11/2018	Cardiology evaluation	EKG: "nonspecific ST/T wave changes" Echocardiogram: WNL Plans to follow up in 1 year with echocardiogram

SCOR
The Art & Science of Risk

Editor
Pam Granzin
704.344.2725
pgranzin@scor.com
www.SCORGlobalLifeAmericas.com

SCOR Global Life | Printed in USA © 2019

CHARLOTTE
101 South Tryon Street
Suite 3200
Charlotte, NC 28280

KANSAS CITY
11625 Rosewood Street
Suite 300
Leawood, KS 66211

MINNEAPOLIS
650 Third Avenue South
Suite 1600
Minneapolis, MN 55402

MONTREAL
1 Place Ville-Marie
Suite 2010
Montréal
QC H3B 2C4
Canada

TORONTO
199 Bay Street
Suite 2800
Toronto
ON M5L 1G1
Canada

MEXICO
Oficina de
Representación
en México
Edificio Torre Reforma
Paseo de la Reforma
483, floor 36
Col. Cuauhtemoc,
06500, Mexico City
Mexico

SANTIAGO
Edificio Isidora
Magdalena Norte
Magdalena 181, Piso 12,
Oficina 1201 Norte
7550055 Las Condes
Santiago, Chile

SAO PAULO
SCOR Global Life
U.S. Re Escritorio de
Representação no
Brasil Ltda
R.Luigi Galvani 70
Suite 121 04575-020
São Paulo, Brazil