Volume 6, Issue 4 • Winter 2011 - 2012

Canadian Journal of General Internal Medicine

LA REVUE CANADIENNE DE MÉDECINE INTERNE GÉNÉRALE

Publications Agreement Number 40025049 | 1911-1606

Practical Approach to Isolated Right-Sided Heart Failure
Bizios and Howlett

Aldosterone Antagonist Therapy in Heart Failure
Barry et al.

www.csimonline.com


“OPINION
IS GOOD.
BUT EVIDENCE
IS BETTER.”*

BRILINTA® ticagrelor tablets

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

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

BRILINTA is contraindicated in patients who: are hypersensitive to this medication or to any ingredient in the formulation, have active pathological bleeding such as peptic ulcer or intracranial hemorrhage, have a history of intracranial hemorrhage, have moderate to severe hepatic impairment or are also taking strong CYP3A4 inhibitors.

BRILINTA should be used with caution in patients with a propensity to bleed (e.g., due to recent trauma, recent surgery, active or recent gastrointestinal bleeding, or moderate hepatic impairment) and in patients requiring oral anticoagulants (e.g., warfarin) and/or fibrinolytics agents (within 24 hours of BRILINTA dosing). Caution should also be used in patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g., non-steroidal anti-inflammatory drugs [NSAIDs]). Co-administration of BRILINTA and high maintenance dose ASA (>150 mg daily) is not recommended.

In the PLATO study, bleeding events associated with BRILINTA vs. clopidogrel included total major (11.6% vs. 11.2%) and combined total major + minor (16.1% vs. 14.6%). When minor bleeding was included, combined PLATO-defined major and minor bleeding events were significantly higher on BRILINTA than on clopidogrel (p=0.0084). There were few fatal bleeding events in the study, 20 (0.2%) for BRILINTA and 23 (0.3%) for clopidogrel. The most common adverse events associated with BRILINTA vs. clopidogrel were dyspnea (12.0% vs. 6.5%), headache (6.5% vs. 5.8%) and nosebleed (6.0% vs. 3.4%).

See the Product Monograph for full contraindications, warnings, precautions, dosing and administration.

Reference: 1. BRILINTA® Product Monograph. AstraZeneca Canada Inc. May 26, 2011.

*Fictitious quote. May not be representative of all healthcare professionals.

AstraZeneca

Member R&D BR032E PAAB 08/12

See prescribing summary on page 158

Canadian Journal of
General Internal Medicine
LA REVUE CANADIENNE DE MÉDECINE INTERNE GÉNÉRALE
Volume 6, Issue 4 • 2011
Publications Agreement Number 40025049

Subscription Rates:
Per year: $15.00; per issue: $3.75

Return undeliverable Canadian Addresses to:
ANDREW JOHN PUBLISHING INC.
115 King St W., Suite 220, Dundas, ON L9H 1V1

Canadian Journal of General Internal Medicine is published four times a year by Andrew John Publishing Inc., with offices located at 115 King Street West, Suite 220, Dundas, ON L9H 1V1.

CONTENTS

Volume 6, Issue 4
2011

Canada

We acknowledge the financial support of the Government of Canada through the Canada Periodical Fund of the Department of Canadian Heritage.

ABOUT THE COVER

This issue's cover photo was taken by J.J. Guy Longtin, a career fire chief who enjoys photography as a way to relieve stress. This photo was captured at the annual powwow of the Pikwàkanagàns of Golden Lake, Ontario.

For Instructions to Authors, please visit
www.andrewjohnpublishing.com/CGJIM/instructionstoauthors.html

CSIM Members of Council

Dr. Maria Bacchus
President
Calgary, AB

Dr. Finlay McAlister
Past-President
Edmonton, AB

Dr. Stephen Hwang
Secretary-Treasurer, Ontario Region Representative
Toronto, ON

Dr. Nadine Lahoud
Quebec Region Representative
LaSalle, QC

Dr. Patrick Bergin
Eastern Region Representative
Charlottetown, PEI

Dr. David Simpson
Eastern Region Representative
Halifax, NS

Dr. Donald Echenberg
Vice-President, Education Committee
Quebec Region Representative
Sherbrooke, QC

Dr. Bert Govig
Vice-President, Health Promotion Committee
Quebec Region Representative
Amos, QC

Dr. Tom Maniatis
Quebec Region Representative
Montreal, QC

Dr. Benjamin Chen
Ontario Region Representative
Napanee, ON

Dr. William Coke
Ontario Region Representative
Toronto, ON

Dr. Ameen Patel
Ontario Region Representative
Hamilton, ON

Dr. Neil Gibson
Western Region Representative
St. Albert, AB

Dr. Amy Hendricks
Western Region Representative
Yellowknife, NT

Dr. Anne Marie PausJenssen
Western Region Representative
Saskatoon, SK

Dr. Ranjani Aiyar
Resident Representative
Calgary, AB

Other CSIM Positions

Dr. Gary Victor
Vice-President, Membership Affairs
Kelowna, BC

Dr. Bill Ghali
Vice-President, Research and Awards Committee
Calgary, AB

Dr. Kathleen Raby
Co-Chair 2012 Annual Meeting Committee
Quebec City, QC

Dr. Jim Nishikawa
Representative on the RCPSC Specialty Committee in Internal Medicine
Ottawa, ON

To contact a member of CSIM Council, please e-mail csim@royalcollege.ca.

Message from the President • Message de la présidente

Maria Bacchus MD

About the Author
Maria Bacchus is an associate professor in the Department of Medicine at the University of Calgary, in Calgary, Alberta. Correspondence may be directed to Maria.Bacchus@albertahealthservices.ca.

Au sujet de l'auteur
Maria Bacchus est professeure agrégée de médecine à la faculté de médecine de l'Université de Calgary en Alberta. Veuillez adresser la correspondance à Maria.Bacchus@albertahealthservices.ca

Dear Colleagues,

I am honoured to be your advocate for general internal medicine (GIM) as the 15th president of the Canadian Society of Internal Medicine. I am excited to hear your input and suggestions as we forge our identity as a subspecialty.

I would like to thank our past-president, Finlay McAlister, for his exemplary leadership as he steered us through groundbreaking changes including the recognition of general internal medicine as a subspecialty.

Special thanks also to David Simpson and the members of the Annual Meeting Committee for the successful organization and implementation of our recent meeting in Halifax, Nova Scotia. Under the guidance of Drs. Nadine Lahoud and Kathleen Raby, we are enthusiastically planning our next Annual Meeting, to be held October 17–20, 2012, in Quebec City, Quebec.

This is an exhilarating time for GIM, and I invite you to use this opportunity to shape the future of our subspecialty. Your suggestions are valuable. We encourage you to make your voice heard. Please email me or your council members at csim@royalcollege.ca.

Cher collègues,

J'ai l'immense privilège de promouvoir les intérêts de la médecine interne générale en votre nom à titre de 15e présidente de la Société canadienne de médecine interne (SCMI). Je suis impatiente de connaître votre opinion, vos idées et vos suggestions alors que la discipline forge son identité de surspécialité.

Je tiens à remercier le président sortant, Finlay McAlister, de son leadership exemplaire durant une période de changement sans précédent qui a débouché notamment sur la reconnaissance de la surspécialité de la médecine interne générale.

Mes remerciements vont également à David Simpson et aux membres du comité du congrès annuel qui ont organisé et tenu de main de maître le dernier congrès à Halifax en Nouvelle-Écosse.

Sous la direction des Dres Nadine Lahoud et Kathleen Raby, nous planifions déjà avec beaucoup d'enthousiasme le prochain congrès qui aura lieu dans la ville de Québec du 17 au 20 octobre 2012.

Nous abordons sans doute l'âge d'or de la médecine interne générale, et je vous invite à participer à cette entreprise fascinante qui consiste à façonner l'avenir de la surspécialité. Nous accordons énormément d'importance à votre opinion et à vos suggestions. N'hésitez surtout pas à les exprimer. Vous pouvez communiquer avec les membres du conseil d'administration ou avec moi par courriel à csim@royalcollege.ca.

CSIM News

The CSIM gratefully acknowledges support of our scientific program by educational grants from:

PLATINUM SPONSORSHIP
Abbott
AstraZeneca
Bayer Healthcare
Eli Lilly Canada
NovoNordisk
Merck

GOLD SPONSORSHIP
Boehringer-Ingelheim
Sanofi Aventis

Thank you to AstraZeneca for their support of the Osler Awards and the Osler Lecture.

I had heard of Health Match BC and had kept their information on file. When the time came I went through their site, looking for a full-time emergency room position in the mountains. That's where we found Nelson – a paradise for backcountry skiing.

Dr. Isabelle Cochrane

ENRICH YOUR CAREER. ENHANCE YOUR QUALITY OF LIFE.

Join the hundreds of physicians who have moved to British Columbia to enjoy a quality of life that is envied around the world. Find out how our physician services team can assist you in matching your lifestyle interests with exciting career opportunities. **Register online today!**

PHYSICIANS | NURSES | ALLIED HEALTH

healthmatchbc.org

FIND A JOB IN BC

Health Match BC is a free health professional recruitment service funded by the Government of British Columbia, Canada

health match bc

TEL: 604.736.5920 • TOLL-FREE: 1.877.867.3061 • EMAIL: welcome@healthmatchbc.org

Practical Approach to the Diagnosis and Management of Isolated Right-Sided Heart Failure

Anna Bizios MD, Jonathan Howlett MD

About the Authors

Anna Bizios is a cardiology fellow in the Department of Cardiac Sciences, University of Calgary, in Calgary, Alberta. Jonathan Howlett is a clinical professor of medicine at the Libin Cardiovascular Institute and University of Calgary. He is a member of the Canadian Cardiovascular Society Heart Failure Guidelines Primary Panel. Correspondence may be directed to howlettjonathan@gmail.com.

Clinical Vignette

A 65-year-old obese, diabetic female was admitted to hospital with symptoms of exercise intolerance, shortness of breath on exertion, weight gain, and edema. She had suffered a myocardial infarction (MI) 2 years previously and was on appropriate medical therapy. She was known to have stage 3 diabetic kidney disease.

On admission, she had the following vitals: heart rate 80 beats per minute, blood pressure 155/95 mm Hg, and oxygen saturation 96% on room air. She was obese (body mass index 35 kg/m^2), had 6 cm jugular venous distension, and had moderate peripheral edema. Her heart sounds were normal, but a fourth heart sound was present. She also had a right ventricular heave. Auscultation of the chest was normal, and because of obesity, hepatomegaly was not evident clinically. An electrocardiogram (ECG) revealed sinus rhythm, right atrial enlargement, right ventricular hypertrophy, and old inferior Q waves. She was treated with intravenous furosemide 40 mg/d, and she lost 5 kg over the next 4 days. She then developed dizziness when standing, worsening lethargy, and ongoing shortness of breath. She had a postural drop in systolic blood pressure (110 mm Hg lying and 90 mm Hg standing). Her serum creatinine rose from 160 to 245 mmol/L. Her chest radiograph showed cardiomegaly only. Her urinary protein excretion was 600 mg protein per day. Her complete blood count was unremarkable, and her electrolytes remained within the normal range.

An echocardiogram showed a dilated right ventricle (RV) with septal flattening and a right ventricular systolic pressure (RVSP) of 45 mm Hg (but acoustic windows were poor because of obesity). There was no valvular dysfunction, but inferior wall hypokinesis was evident. A right heart catheterization showed a pulmonary artery (PA) pressure of 78/36 mm Hg and a mean pulmonary capillary wedge pressure (PCWP) of 10 mm Hg. A Persantine MIBI scan showed an old inferior MI, no ischemia, and normal LV (left ventricle) function. A subsequent investigation confirmed the presence of severe obstructive sleep apnea. Her condition improved following the introduction of continuous positive airway pressure (CPAP) therapy.

Discussion

Heart failure is an important clinical syndrome affecting the Canadian population: an estimated 500,000 individuals are living with the disease, and another 50,000 patients are newly diagnosed each year.[1] A significant proportion of these individuals suffer from right-sided heart failure (RHF), which is an independent predictor of mortality in patients with heart failure and may occur as part of the biventricular heart failure syndrome or in the absence of left-sided heart failure (LHF).[2] Isolated RHF (iRHF) frequently occurs as a consequence of a unique set of causes and should be treated differently. Thus, recognition of iRHF is essential. A practical approach to the diagnosis and management of RHF is outlined below.

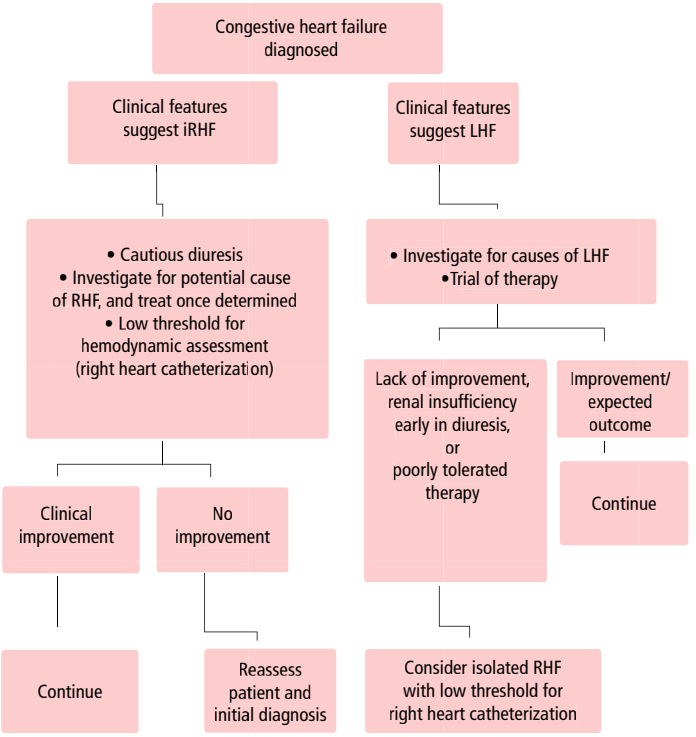


Figure 1. Generalized approach to congestive heart failure. iRHF = isolated right-sided heart failure; LHF = left-sided heart failure; RHF = right-sided heart failure.

Step 1: Making the Diagnosis of Heart Failure

iRHF generally refers to the clinical presentation of signs and symptoms of heart failure without the specific findings of LHF. This means the patient's clinical condition is not due to elevated left-sided filling pressures, which can be difficult to demonstrate without invasive assessments. The first step in the identification of iRHF is the diagnosis of heart failure in general (Figure 1 and Table 1). During the initial clinical assessment, clues may be present to suggest RHF in the absence of left-sided involvement. For example, a history of long-standing chronic obstructive pulmonary disease or other severe lung disease may be elicited. Symptoms such as fatigue, abdominal distension, or anorexia in the absence of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea should raise suspicions for RHF. On physical examination, predominant right-sided findings (e.g., pulsatile liver, ascites, elevated jugular venous pulsation with Kussmaul's sign) may be present without pulmonary crackles. A chest radiograph may fail to show pulmonary congestion or LV

Table 1. Signs and Symptoms Suggestive of Right-Sided Heart Failure

Symptoms	
	Shortness of breath
	Fatigue
	Anorexia or early satiety
	Right upper quadrant discomfort
	Peripheral edema
Signs	
	Elevated jugular venous pulsation
	Positive hepatojugular reflux
	Kussmaul's sign*
	Peripheral edema or ascites
	Hepatomegaly
	Right-sided S3
	Tricuspid regurgitation murmur
	Right ventricular lift

*Kussmaul's sign is observed when the jugular venous pulsation rises on inspiration.

Source: Adapted from the Canadian Cardiovascular Society Heart Failure Guidelines Pocket Card, 2011.

Table 2. BNP or NT-proBNP Reference Levels*

BNP	NT-proBNP
<100 pg/mL, decompensated HF unlikely	<300 pg/mL, decompensated HF unlikely
>500 pg/mL, decompensated HF likely	>900 pg/mL, decompensated HF likely (ages 50–75 y)
	>1,800 pg/mL, decompensated HF likely (age >75 y)

BNP = B-type natriuretic peptide; HF = heart failure; NT-proBNP = N-terminal pro B-type natriuretic peptide.

*Note that renal failure may cause the BNP and NT-proBNP to rise in the absence of heart failure.

Source: Adapted from the Canadian Cardiovascular Society Heart Failure Guidelines Pocket Card, 2011.

dilatation, but signs of RHF may be evident, such as RV enlargement, dilatation of the azygous vein, and an enlarged PA.

One cannot rule out compensated LHF on the basis of a history and physical examination alone. In fact, up to 25% of patients with congestive heart failure have a normal chest radiograph upon initial assessment.[3] Transthoracic echocardiography (TTE) should be used routinely to assess cardiac chamber size and function in patients with heart failure. In the setting of iRHF, TTE will confirm two major points: (1) a lack of evidence of increased left ventricular filling pressures, systolic dysfunction, or valvular disease and (2) evidence of abnormal right ventricular size, function, right-sided valvular heart disease, or filling pressures. An elevated B-type natriuretic peptide (BNP) or NT-proBNP is frequently seen (Table 2) but is usually lower than values observed in LHF.[4] Once the diagnosis is made, attention must be turned to determining the underlying etiology of iRHF.

An important clinical clue to the presence of iRHF is the lack of symptomatic improvement in patients despite diuresis. Additionally, patients may demonstrate systemic hypotension or worsening renal function despite evidence of elevated right-sided filling pressures. A clinician may be alerted to iRHF only after unsuccessful initial therapy for presumed LHF.

Step 2: Identifying the Etiology of RHF

Identifying the cause of RHF should be approached from two perspectives. Firstly, the clinician should obtain an assessment of the cardiac structures and hemodynamics. Secondly, potential non-cardiac etiologies should be investigated with ancillary testing.

In addition to traditional assessment, the TTE should include an attempt to find evidence of increased LV filling pressures or diastolic dysfunction, especially if the LV ejection fraction is >40%. If the TTE reveals an enlarged PA, a dilated RV, and no significant tricuspid or pulmonary regurgitation (particularly in the presence of a right bundle branch block on electrocardiography), an atrial septal defect (ASD) should be excluded via transesophageal echocardiography (TEE). A high-quality TTE does not exclude the presence of an ASD.

Further imaging with cardiac computed tomographic angiography allows for the assessment of cardiac function, valvular or pericardial involvement, and any coronary artery disease that may be contributing to iRHF. Alternatively, cardiac magnetic resonance imaging can be tailored to specific disease states such as RV infarction, congenital heart disease, pulmonary arterial hypertension (PAH), and arrhythmogenic right ventricular cardiomyopathy (ARVC).[5] Interestingly, while cardiac ischemia commonly presents with diastolic LHF, it is rarely seen as a cause of iRHF,[6] so cardiac ischemic work-up is less of a priority in the absence of demonstrable left ventricular dysfunction.

Despite advances in non-invasive cardiac imaging, several studies have shown that echocardiographically derived estimates of RVSP are incorrect in more than 30% of cases.[7] Right heart catheterization continues to play a critical role in the assessment of heart failure – in particular the measurement of PA pressure and PCWP. It is often required to accurately quantify the extent of hemodynamic disruption and to confirm pulmonary arterial hypertension (PAH), which is defined by a mean PA pressure greater than 25 mm Hg at rest. It is the gold standard for diagnosing *cor pulmonale*, which refers specifically to RHF caused by PAH. If clinical assessment and non-invasive imaging have failed to yield a definitive diagnosis for iRHF, prompt referral for right heart catheterization is recommended.

Additional non-cardiac testing should be selected based on clinical suspicion. Severe lung disease such as obstructive sleep apnea (OSA), chronic thromboembolic disease, and restrictive lung disease can cause sufficiently high PA pressures to cause RHF; if only mild or moderate pulmonary disease is present, a different etiology must be sought. Ancillary tests may include, but are not limited to pulmonary function testing, chest CT, ventilation-perfusion scans, polysomnography, and arterial blood gases. Systemic disorders known to cause RHF, such as sickle cell disease, thalassemia major, and connective tissue disorders, should be considered and investigated if supported by the clinical picture. Uncommonly, poor RV function without an obvious underlying cause may be due to ARVC, which may be familial.

Step 3: Treating RHF

The management of RHF depends on whether it is isolated or secondary to LHF. If present, treatment of this condition should be initiated according to the published guidelines. Conversely, the management of isolated RHF is largely empiric, with few randomized studies available for guidance. Diuretics are widely employed to treat fluid retention but must be used judiciously to maintain adequate LV filling pressures. ACE inhibitors, beta-blockers, and

Table 3. Clinical Pearls Relating to RHF

The chest radiograph may be negative for pulmonary edema in up to 25% of patients presenting with congestive heart failure.[3]
Doppler echocardiography frequently yields inaccurate estimates of PA pressure and cardiac output in the evaluation of pulmonary hypertension.[7]
BNP levels rise in isolated RHF, though generally not as high as in LHF. Values typically rise to 300–400 pg/mL, in comparison to LHF values of >700–1,100 pg/mL for those presenting with acute symptoms.[4]
Although classically involving the RV alone, some involvement of the LV has been found in >80% of subjects in a cohort study of familial ARVC.[9]
Only severe pulmonary disease can cause iRHF – in a patient with mild or moderate lung disease, a different etiology for iRHF must be sought.
In an elderly female with iRHF and tricuspid regurgitation, OSA should be considered and investigated if supported by the clinical picture.
RV dilatation with right bundle branch block on ECG should raise concern for an ASD until proven otherwise. A TEE should be performed to rule out an ASD.
Ventilation-perfusion lung scans should be preferred over helical computed tomographic pulmonary angiography for the diagnosis of chronic thromboembolic disease in patients with pulmonary hypertension (sensitivity of 96% versus 51%, respectively).[10]
Constrictive pericarditis can cause signs and symptoms similar to RHF: peripheral edema, ascites, and liver congestion are common presentations. The TTE may be reported as normal unless specific respiratory variations in tricuspid and mitral inflows are requested.
If hypotension and pre-renal azotemia develop during early diuresis of presumed LHF, RHF should be strongly considered.

ARVC = arrhythmogenic right ventricular cardiomyopathy; BNP = B-type natriuretic peptide; ECG = electrocardiogram; iRHF = isolated right-side heart failure; LHF = left-side heart failure; LV = left ventricle; OSA = obstructive sleep apnea; PA = pulmonary artery; RHF = right-side heart failure; RV = right ventricle; TTE = transthoracic echocardiography.

digoxin have no proven benefit. An effort should be made to maintain normal sinus rhythm whenever possible as many patients with RHF do not tolerate loss of atrioventricular synchrony.

Individualized treatment regimens must also target the underlying cause of RHF. For example, therapeutic options for primary PAH may include prostanoids, endothelin receptor blockers, phosphodiesterase-5 (PDE-5) inhibitors, and anticoagulation.[8] Because access to these treatments is limited, referral of such patients to a pulmonary hypertension clinic is suggested. Thromboembolic disease is treated with systemic anticoagulation. An acute pulmonary embolus that is hemodynamicallly significant may also be amenable to thrombolysis. Pulmonary endarterectomy may play a role in the treatment of chronic thromboembolic pulmonary hypertension. OSA may be managed with weight loss and CPAP. Congenital or valvular disorders may require surgical intervention. Patients with ARVC may be at high risk for sudden death and require referral to a centre with experience in treatment of this disorder.

Recently, there has been investigation into two specific therapies targeting the RV: PDE-5 inhibitors and metabolic modulators.[8] In brief, it has been noted that PDE-5 inhibitors increase contractility in the hypertrophied RV of rats, separate from the effect of increased PA dilation and decreased PA remodelling. Indeed, clinical trials of PDE-5 inhibitors in patients with LV systolic dysfunction and pulmonary hypertension refractory to standard therapy suggest that improvements in PA pressure, exercise tolerance, and HF symptoms may result. Metabolic modulation by the molecule dichloroacetate has also been found to increase RV inotropy and decrease PA remodelling. While these therapies are being further researched, it is hopeful that RV-specific treatments will provide a breakthrough in the management of RHF. Clinical pearls relating to RHF are presented in Table 3.

Conclusion

The diagnostic approach to RHF begins with the identification of the failing RV in the setting of a normally functioning left heart. Thereafter, the choice of advanced cardiac imaging and ancillary non-cardiac testing must be tailored to the individual patient. The role of right heart catheterization, however, should not be underestimated in obtaining an accurate assessment of cardiac and pulmonary hemodynamics.

While the management of RHF is largely empiric, new therapeutic modalities are being developed. Currently, cautious diuresis, the maintenance of sinus rhythm whenever possible and the management of the underlying cause remain the mainstay of therapy for RHF.

References

1. Ross H, Howlett J, Arnold JMO, et al. Treating the right patient at the right time: access to heart failure care. Can J Cardiol 2006;22:749–54.
2. Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 2001;37:183–8.
3. Fonseca C, Mota T, Morais H, et al. The value of the electrocardiogram and chest x-ray for confirming or refuting a suspected diagnosis of heart failure in the community. Eur J Heart Fail 2004;6:807–12.
4. Hobbs RE. Using BNP to diagnose, manage, and treat heart failure. Cleve Clin J Med 2003;70:333–6.
5. Goetschalckx K, Rademakers F, Bogaert J. Right ventricular function by MRI. Curr Opin Cardiol 2010;25:451–5.
6. Haji SA, Movahed A. Right ventricular infarction – diagnosis and treatment. Clin Cardiol 2000;23:473–82.
7. Fisher MR, Forfia PR, Chamera E, et al. accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009;179:615–21.
8. Haddad F, Ashley E, Michelakis ED. New insights for the diagnosis and management of right ventricular failure, from molecular imaging to targeted right ventricular therapy. Curr Opin Cardiol 2010;25:131–40.
9. Sen-Chowdhry S, Syrris P, Ward D, et al. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. Circulation 2007;115:1710.
10. Tunarin N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med 2007;48:680.

1-877-522-9722
physicianrecruitment@interiorhealth.ca
Interior Health

Cranbrook
Kamloops
Nelson
Vernon
Williams Lake

Life's better here for...

Internists

Credibility. Compassion. Caring.

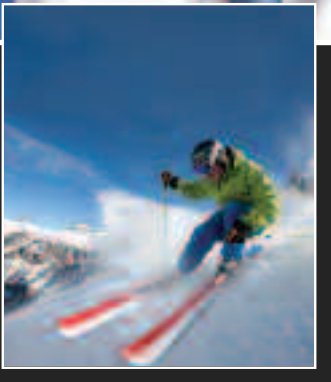
My work is gratifying. My patients are flourishing. So is my family.

Kids love it – biking, skiing, fishing. The outdoor opportunities are endless. I've traded rush hour for time with my family.

It's a perfect balance between caring and carefree.

Interior Health is seeking General Internists and an Internal Medicine/Respirologist for several communities throughout BC's sunny interior. May be eligible for additional incentives. Must be eligible for licensure in BC.

Communities within Interior Health offer exceptional outdoor recreational opportunities such as skiing, snowmobiling, hiking, mountain biking, golfing and fishing.



Life's better here. Find out why.

betterhere.ca

Le lymphome intravasculaire: une pathologie sournoise et agressive à inclure dans le diagnostic différentiel d'une fièvre d'étiologie indéterminée

Maxime Berthelot-Richer MD, Chantal Vallée MD, Rabia Temmar MD, Hans Knecht MD, Rami Kotb MD, Martine Chamberland MD

À propos des auteurs
Maxime Berthelot-Richer est résident en cardiologie à l'Université Laval. Il a fait son tronc commun de médecine interne à la Faculté de médecine et des sciences de la santé de l'Université de Sherbrooke. Martine Chamberland est interniste au Centre Hospitalier Universitaire de Sherbrooke (CHUS). Chantal Vallée est interniste à l'Hôpital Charles LeMoyne. Rabia Temmar est pathologiste au CHUS. Hans Knetch est hématologue au CHUS. Rami Kotb est hématologue au CHUS. Martine Chamberland, Chantal Vallée, Rabia Temmar, Hans Knetch, et Rami Kotb sont aussi professeurs à la Faculté de médecine et des sciences de la santé, Université de Sherbrooke. Correspondance peut être envoyé à maxime.berthelot-richer.1@ulaval.ca.

La fièvre d'étiologie indéterminée (FEI) est un problème clinique fréquemment rencontré par l'interniste. Le lymphome intravasculaire (LIV) est une forme rare et agressive de lymphome non-hodgkinien extra-nodal[1]. La maladie est limitée à la microcirculation, sans masse tumorale détectable. La fièvre prolongée avec ou sans autres symptômes B en est souvent la manifestation initiale[2]. Un diagnostic rapide est important car il existe un traitement curatif potentiel[3–5]. Malheureusement, la présentation non spécifique, l'absence de masse tumorale détectable, la rareté de cette pathologie et sa méconnaissance de la part des cliniciens font en sorte que la majorité des diagnostics sont faits tardivement, voire en post-mortem[3,6]. Nous rapportons dans cet article deux cas de lymphomes intravasculaires ayant eu comme manifestation principale une fièvre d'étiologie indéterminée. Ces cas illustrent à la fois les atteintes fréquentes de cette entité, les pièges et les avenues diagnostiques de même que l'évolution fatale lorsque non reconnue précocement.

Premier cas

Une femme de 79 ans, sans antécédent pertinent, se présente à l'urgence pour un tableau de fièvre vespérale évoluant depuis 1 semaine accompagnée d'une diminution de son état général. L'histoire et l'examen physique sont par ailleurs non révélateurs. Le bilan démontre un syndrome inflammatoire important avec une vitesse de sédimentation (VS) à 70 mm/h, une protéine C réactive à 180 mg/L, de même qu'une anémie normochrome normocytaire arégénérative à 88 gr/dl qui progressera et nécessitera dès lors la transfusion d'un culot globulaire sur une base hebdomadaire. On note également une augmentation des lactates déshydrogénase (LDH) à 450 UI/L (N <250). Le bilan microbiologique exhaustif est négatif. Le bilan immunologique est également entièrement négatif, de même qu'une biopsie de l'artère temporale. La biopsie de moelle osseuse (BMO) met en évidence une cellularité augmentée et une dysplasie médullaire. La tomographie axiale de l'abdomen démontre une légère hépatomégalie à 18 cm et la rate est mesurée à 12 cm. Une tomodensitométrie par émission de positrons (TEP) démontre un hypermétabolisme léger et non spécifique de la moelle osseuse et de la rate.

Un diagnostic par défaut de syndrome inflammatoire possiblement secondaire à une vasculite systémique est posé et un traitement avec de la prednisone à 1 mg/kg est institué. La fièvre s'amende et du méthotrexate 15 mg sc par semaine est introduit pour consolider le traitement et permettre la décroissance de la corticothérapie. Cependant, après une amélioration transitoire de son état général, la patiente se redétériore au cours des 2 mois suivants. Son poids passe de 96 à 76 kilogrammes. Elle développe des troubles cognitifs, une polyneuropathie axonale sensitivo-motrice des 4 membres, un anasarque et une hyponatrémie suggestive d'un SIADH. La ferritine, initialement à 300 µg/L, est maintenant à 5300 µg/L. Le dosage des triglycérides est à 2,19 mmol/L et le fibrinogène est à 8,6 g/L. Le dosage de la bêta-2-microglobuline à 724 nmol/L.

Devant ces nouveaux éléments, le diagnostic de lymphome intravasculaire est évoqué. Le TEP/CT scan de contrôle est entièrement normal. La BMO de contrôle ne démontre pas d'infiltration lymphomateuse ni d'hémophagocytose. L'examen cutané est sans particularité hormis un érythème plantaire bilatéral non spécifique. Des biopsies cutanées incluant l'hypoderme sont effectuées sur peau saine au niveau de la cuisse et de l'abdomen. L'analyse pathologique démontre une infiltration des petits capillaires par des immunoblastes de phénotype B et confirme le diagnostic de lymphome intravasculaire (Figure 1). La patiente étant grabataire, elle opte pour des soins de confort et décède dans les jours suivants.

Deuxième cas

Un homme de 65 ans est transféré d'un hôpital périphérique pour une fièvre évoluant depuis un mois accompagnée de fatigue et sudation nocturne profuse. Il se plaint aussi de troubles neurologiques, rapportant notamment des paresthésies et une faiblesse progressive des membres inférieurs ainsi que des troubles d'équilibre et une difficulté à la marche. Finalement, il rapporte un tableau douloureux dorsolombaire. À l'examen, on objective une atteinte de la pallesthésie et de la proprioception aux membres inférieurs. Le reste de l'examen est sans particularité. Le bilan démontre une pancytopénie (GB: $1{,}2 \times 10^9$/L; neutrophiles: $0{,}400 \times 10^9$/L; Hb: 97 g/L; Plt: 75×10^9/L). La protéine C réactive est élevée à 100 mg/L et les LDH sont à 800 UI/L. Le bilan microbiologique extensif ne met en évidence aucune infection et le bilan immunologique est négatif. La biopsie de moelle, hormis une légère hyperplasie de la lignée érythroïde, est sans particularité.

Un bilan radiologique démontre une splénomégalie à 18 cm. Le TEP scan révèle un métabolisme augmenté de la surrénale gauche et une discrète captation aux apex pulmonaires. Une cytoponction de la surrénale gauche est effectuée et oriente vers le diagnostic d'un phéochromocytome mais cette hypothèse est éliminée par une scintigraphie au MIBG et une recherche de catécholamines et métanéphrines urinaires qui s'avèrent négatives.

La résonnance magnétique (IRM) cérébrale démontre une augmentation de volume de la tige hypophysaire. Une IRM dorsolombaire démontre de petites anomalies de signal à divers niveaux. Un électromyogramme (EMG) met en évidence une polyneuropathie axonale à prédominance sensitive.

Une neurosarcoïdose est évoquée comme diagnostic de travail. Le patient est mis sous prednisone 1,5 mg/kg et on note immédiatement une amélioration de son état général de même qu'une résolution de la fièvre. Il reçoit son congé.

Il revient un mois plus tard avec récidive de température et détérioration

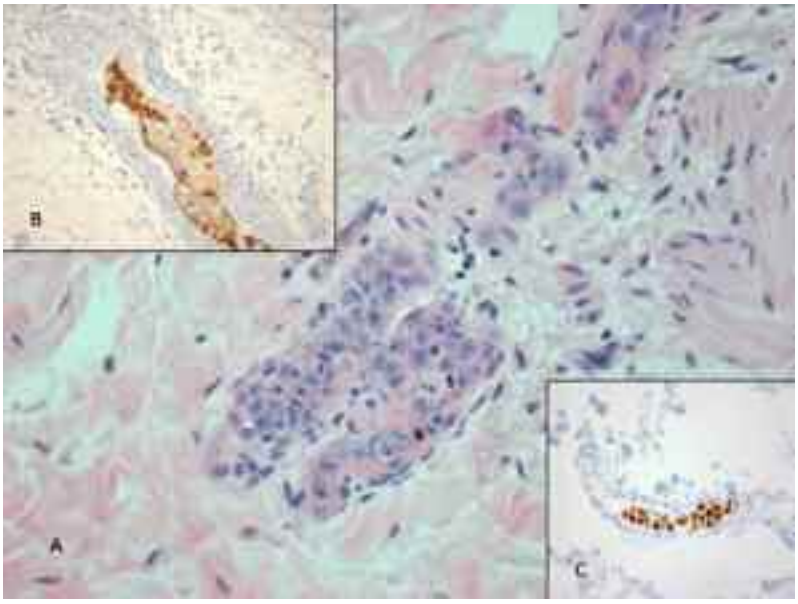


Figure 1. Lymphome B à grandes cellules intravasculaire. *A*, Capillaires du derme en peau saine distendus par des cellules tumorales occupant l'espace intravasculaire (HE ×400). *B*, Les cellules tumorales sont positives pour le marqueur CD20 (×200). *C*, Les cellules sont également positives pour le marqueur MUM1 (×400).

de son état caractérisée par une perte de poids, un oedème des membres inférieurs important et une incontinence urinaire et fécale nouvelle. Durant l'hospitalisation, une acidose lactique sévère inexpliquée (jusqu'à 15 mmol/L) est présente en l'absence d'hypotension ou d'hypoperfusion clinique. Les paresthésies, la faiblesse des membres inférieurs et la pancytopénie progressent. Un tableau confusionnel fluctuant est noté. Une éruption papuleuse violacée apparaît au niveau du tronc. Une biopsie cutanée de ces lésions démontre une infiltration des capillaires par des immunoblastes B, compatible avec le diagnostic de lymphome intravasculaire. Le patient décède cette même journée d'insuffisance multiorganique.

Discussion

Le lymphome intravasculaire est un sous-type rare de lymphome extra-nodal non-hodgkinien diffus à grandes cellules. La plupart des cas sont de phénotype B. Cette entité se distingue par sa prolifération cellulaire presque exclusivement limitée à la lumière des capillaires. Depuis sa description en 1959[7], un peu plus de 300 cas ont été rapportés dans la littérature.

Deux sous-types cliniques existent: la forme asiatique, caractérisée par une association forte avec le syndrome hémophagocytaire et un envahissement de la moelle osseuse, et la forme occidentale, qui présente moins fréquemment ces particularités mais davantage d'atteinte neurologique.

Au sujet de la forme occidentale, l'âge moyen au diagnostic est de 70 ans[2]. La maladie se présente de façon agressive et est généralement disséminée au moment du diagnostic. La majorité des patients présentent des symptômes B, notamment de la fièvre[2]. L'atteinte cutanée est fréquente, quoique très hétérogène. La plus classique est une éruption papuleuse violacée. Près du tiers des patients présentent dans leur évolution des atteintes neurologiques multifocales rapidement progressives, centrales ou périphériques[2]. Des infiltrations de la microcirculation pulmonaire, hépatique et rénale sont aussi possibles avec ou sans défaillance multiorganique. Des atteintes endocriniennes variées, y compris le SIADH et l'infiltration de la tige hypophysaire, ont également été rapportées[8].

Au bilan, une augmentation des LDH ou de la bêta-2-microglobuline est observée dans plus de 80% des cas[2]. On retrouve généralement une anémie normocytaire arégénérative et un syndrome inflammatoire.

Le diagnostic de cette pathologie peut s'avérer ardu. D'une part, il n'y a généralement pas de masse tumorale détectable puisque les cellules néoplasiques prolifèrent quasi exclusivement dans la lumière des capillaires. Contrairement à la majorité des autres lymphomes, la biospie de moelle, le frottis périphérique et le TEP/CT scan sont souvent négatifs. Avec ses manifestations variées, cette pathologie peut mimer diverses autres affections[9]. Elle est parfois confondue avec une vasculite systémique ou du système nerveux central, puisqu'elle entraîne des foyers ischémiques multifocaux.

En l'absence de lésions cutanées visibles, des biopsies en peau saine peuvent permettre de poser précocement le diagnostic[10,11]. Les spécimens biopsiques doivent inclure l'hypoderme car cette zone semble préférentiellement affectée[11]. Les sites à privilégier sont les cuisses et l'abdomen. Le nombre exact de biopsies nécessaire au diagnostic n'est pas connu mais il est recommandé d'en faire plusieurs[12]. Alternativement, une biopsie d'un organe atteint, notamment la biopsie cérébrale, peut mener au diagnostic.

Le traitement de cette pathologie inclut une chimiothérapie à base d'anthracycline, plus souvent un régime CHOP[1]. Malheureusement, le pronostic reste sombre compte tenu du caractère d'emblée disséminé de la maladie et de la fréquence des récidives. L'utilisation du rituximab a récemment apporté de bons résultats avec quelques guérisons dans des rapports de cas réfractaires au CHOP et ouvre la voie vers de meilleurs succès thérapeutiques[4,5].

Conclusion

Le lymphome intravasculaire est une entité à suspecter chez les patients avec une FEI qui demeure sans diagnostic après un bilan habituel. Les atteintes cutanées ou neurologiques sont à rechercher. Un syndrome inflammatoire, l'augmentation des LDH, de la bêta-2-microglobuline et une anémie doivent orienter le clinicien vers ce diagnostic. En l'absence de lésions cutanées à l'examen, des biopsies multiples en peau saine au niveau des cuisses et de l'abdomen doivent être obtenues afin de poser rapidement le diagnostic et de proposer au patient un traitement potentiellement curatif.

Bibliographie

1. Gatter KC, Warnke RA. Intravascular large B-cell lymphoma. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press, 2001:177–8.
2. Ferreri A, Campo E, Seymour J, et al. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the cutaneous variant. B J Haematol 2004;127:173–83.
3. Ponzoni M, Ferreri AJ, Campo E, et al. Definition, diagnostic, and management of intravascular large B-cell lymphoma: proposals and perspectives from an international consensus meeting. J Clin Oncol 2007;25(21):3168–73.
4. Bashenova L, Higginbottom P, Mason J. Intravascular lymphoma: a role for single-agent rituximab. Leuk Lymphoma 2006;47(2):337–41.
5. Shimada K, Matsue K, Yamamoto K, et al. Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL group in Japan. J Clin Oncol 2008;26:3189–95.
6. Bozzoli V, Chiara M, D'Alo F, et al. Intravascular large B cell lymphoma: when lymphoma is suspected but routine diagnostic work-up is negative. Leuk Lymphoma 2009;50(11):1900–3.
7. Pfleger L, Tappeiner J. On the recognition of systematized endotheliomatosis of the cutaneous blood vessels (reticuloendotheliosis). Hautarzt 1959;10:359–63.
8. Kraus M, Jones D, Bartlett N. Intravascular lymphoma associated with endocrine dysfunction: a report of four cases and a review of the literature. Am J Med 1999;107:169–76.
9. Anastasi J. Another great medical mimic: intravascular lymphoma. Leuk Lymphoma 2009;50(11):1742–3.
10. Asada N, Odawara J, Kimura S, et al. Use of random skin biopsy for diagnosis of intravascular large B-cell lymphomas. Mayo Clinc Proc 2007;82:1525–7.
11. Kiyohara T, Kumakiri M, Kobayashi H, et al. A case of intravascular large B-cell lymphoma mimicking erythema nodosum: the importance of multiple skin biopsies. J Cutan Pathol 2000;27:413–8.
12. Gill S, Melosky B, Haley L, ChanYan C. Use of random skin biopsy to diagnose intravascular lymphoma presenting as fever of unknown origin. Am J Med 2003;114:56–8.

CSIM News

The Canadian Society of Internal Medicine congratulates...

Dr. William Ghali, Calgary, Alberta, for winning the 2011 Dr. David Sackett Senior Investigator Award.
Dr. Ayelet Kuper, Toronto, Ontario, for winning the 2011 New Investigator Award.
Dr. Martha Spencer, Vancouver, British Columbia, for being the recipient of the 2011 Hui Lee Health Promotion Scholarship.
Dr. Jane Lemaire, Calgary, Alberta, as the 2011 CSIM/Royal College Osler Lecturer.

The recipients of the CSIM Osler Awards:

Dr. Hector Baillie, Nanaimo, British Columbia
Dr. Daniel Panisko, Toronto, Ontario
Dr. Barrie Phillips, Terrace, British Columbia
Dr. Belluru S. Satyanarayana, Bathurst, New Brunswick
Dr. Mark Whalen, Campbellton, New Brunswick

Ted Giles Clinical Vignettes

Congratulations to the winners of the 2011 Ted Giles Clinical Vignettes Prize Competition:

First Place:	**Dr. Benjamin Sehmer,** University of Saskatchewan "Soda Induced Paralysis: A Case of Graves' Disease Presenting as Thyrotoxic Periodic Paralysis
Second Place:	**Dr. Karen Okrainec,** McGill University "POEMS syndrome: finding rhyme and reason in a complex, debilitating and uncommon diagnosis"
Third Place (tie):	**Dr. Julie Gilmour,** Queen's University "A Diagnostic Challenge: Cushing's in Pregnancy"
Third Place (tie):	**Dr. Faizan Amin,** McMaster University "A Young Man with Lymphadenopathy, Atrio-ventricular Block, and a Potentially Reversible Cause of Heart Failure"

Awards for Excellence in Research

Congratulations to the winners of the 2011 CSIM/CAPM Research Awards.

Oral Research Presentations

First Place:	**Dr. Alexander Leung,** Brigham & Women's Hospital, Harvard Medical School "Impact of Vendor Computerized Physician Order Entry in Community Hospitals"
Second Place:	**Dr. Anita Au,** University of Alberta "Preoperative Use of Thienopyridines and Outcomes After Surgery: A Systematic Review"
Third Place:	**Dr. Guillaume Babin,** Laval University "Adaptive Servo-Ventilation in Patients with Heart Failure and Sleep Apnea : A Systematic Review and Meta-Analysis"

Poster Research Presentations

First Place:	**Dr. David Campbell,** University of Calgary "The Effect of Primary Care Networks on Diabetes in Alberta's Underserved Populations"
Second Place:	**Dr. Malcolm Wells,** University of Western Ontario "Vasoactive Medications for the Treatment of Acute Variceal Bleeds: A Systematic Review And Meta-Analysis"
Third Place:	**Dr. Alison Walzak,** University of Calgary "Development of a Comprehensive Set of Assessment Tools for Evaluation of Procedural Skills in Internal Medicine"

Aldosterone Antagonist Therapy in Heart Failure: The Trilogy of Trials!

Arden Barry PharmD, Glen J. Pearson PharmD, Sheri L. Koshman PharmD

About the Authors

Arden Barry (far left) is a postdoctoral clinical pharmacotherapy practice fellow in cardiology, Glen J. Pearson an associate professor of medicine, and Sheri Koshman an assistant professor of medicine, all at the Mazankowski Alberta Heart Institute, University of Alberta, in Edmonton, Alberta. Correspondence may be directed to arden.barry@ualberta.ca.

Background

Hollywood seems to have run out of original ideas. Nowadays, the only thing better than a blockbuster movie is an even bigger blockbuster sequel. There was a time when sequels were rare; now, it seems like all successful movie franchises are composed of at least a trilogy. If one is good, then three or four are bound to better. In health care research, clinical trials investigating heart failure (HF) treatment are not devoid of a similar outcome. When the results of the first trials demonstrating the benefits of angiotensin-converting enzyme (ACE) inhibitors and β-blockers in HF were published, the number of subsequent trials involving different agents multiplied rapidly. Surprisingly, aldosterone antagonists did not follow suit after the publication of the results of the Randomized Aldactone Evaluation Study (RALES), which demonstrated a significant benefit in mortality with spironolactone.[1] Between 1999 and 2010, only two studies were published. How could a treatment with such promise be denied the spotlight for so long? Recently, a third installment in the saga of aldosterone antagonist therapy in HF was published: the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF).

The treatment of HF has evolved dramatically over the past 50 years. In the 1960s, standard treatment consisted of salt restriction, digitalis, thiazide diuretics, and strict bed rest.[2,3] Around that time, it was postulated that a novel pharmacologic agent, spironolactone, could potentially benefit patients with refractory HF by blocking aldosterone-mediated retention of sodium and water. Initial case reports demonstrated conflicting evidence with regard to efficacy when spironolactone was dosed at 400–600 mg per day in combination with thiazide diuretics.[2,3] Undeterred, researchers demonstrated additional physiologic benefits of spironolactone beyond the renin-aldosterone-angiotensin system, such as inhibiting cardiac fibroblast proliferation, thereby prohibiting and reversing cardiac remodelling.[4] However, the clinical use of spironolactone in HF was limited until 1999.

RALES was the first large-scale randomized controlled trial to be conducted with spironolactone among patients with HF.[1] The trial enrolled 1,663 patients with systolic HF (left ventricular ejection fraction [LVEF] ≤35% [mean 26%]) and New York Heart Association (NYHA) class III–IV symptoms. Concurrent pharmacologic therapy included ACE inhibitors and loop diuretics. The rate of β-blocker use was low (10%), as the trial was conducted in the era prior to this medication's being recommended for standard use in HF. The trial compared spironolactone 25–50 mg (mean dose 26 mg) daily to placebo for a period of 24 months. The results demonstrated benefit in the primary outcome of death from any cause (34.5% vs. 45.9%; hazard ratio [HR] 0.70 [95% CI 0.60–0.82]) as well as the secondary end points of death and hospitalization from cardiac causes. Although there was a high rate of reported adverse events in both groups, the only significant one was gynecomastia in men (10% vs. 1%, $p < .001$) in the spironolactone group. Serious hyperkalemia (≥6.0 mmol/L) was rare and not different between groups; however, patients with significant renal impairment (serum creatinine >221 μmol/L) or hyperkalemia (serum potassium >5.0 mmol/L) were excluded from the study. This singular trial led to the recommended use of spironolactone in patients with NYHA class III–IV HF, which remained essentially unchanged and unchallenged for the following 11 years. However, the inevitable sequel saw a new protagonist, eplerenone, arrive on the scene.

Eplerenone

Eplerenone is a more selective aldosterone antagonist that was introduced to the Canadian market in 2009. On the basis of the results of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS; Table 1), it is currently indicated as adjunctive therapy for patients with systolic dysfunction (LVEF ≤40%) after acute myocardial infarction (MI).[5]

EPHESUS

The first large randomized controlled trial involving eplerenone was EPHESUS, which compared eplerenone 25–50 mg daily to placebo in 6,632 patients within 3 to 14 days of an acute MI (LVEF ≤40% [mean 33%]) and clinical evidence of HF.[6] Patients with diabetes were included if they met the LVEF criteria without evidence of HF due to their increased risk of cardiovascular (CV) events. Patients were treated concomitantly with appropriate medical therapy for MI and were observed for 16 months. The two primary outcomes – death from any cause (absolute risk reduction [ARR], 2.3%; relative risk [RR] 0.85 [95% CI 0.75–0.96]) and the composite of CV death and first CV hospitalization (ARR 3.3%; RR 0.87 [95% CI 0.79–0.95]) – were both significantly improved with eplerenone. Hyperkalemia (≥6.0 mmol/L) occurred more commonly with eplerenone (5.5% vs. 3.9%, $p = .002$) but no difference was seen in the rate of gynecomastia. This was the first trial to highlight the role of eplerenone in patients with HF post MI.

EMPHASIS-HF

In 2011, the trilogy of aldosterone antagonist trials in HF was completed with the publication of the EMPHASIS-HF results. This randomized, multicentre, double-blind, placebo-controlled trial compared eplerenone 25–50 mg daily (mean dose, 39 mg) to placebo in patients aged ≥55 years with systolic HF (LVEF ≤30%) and NYHA class II symptoms.[7] Patients

Table 1. Summary of Trials of Aldosterone Antagonist Therapy in Patients with Heart Failure

Trial	Design	*N*	LVEF (Mean)	NYHA Class	Intervention	Follow-Up	Outcomes
EMPHASIS-HF	R, P, DB, PC	2,737	≤30% (26%)	I and II	Eplerenone 25 mg PO daily (increased to 50 mg PO daily if K ≤5.0 mmol/L after 4 weeks)	21 mo (median)	All-cause mortality: 12.5% vs. 15.5%, HR 0.76 (95% CI 0.62–0.93) CV death: 10.8% vs. 13.5%, HR 0.76 (95% CI 0.61–0.94) All-cause hospitalization: 29.9% vs. 35.8%, HR 0.77 (95% CI 0.67–0.88) HF hospitalization: 12.0% vs. 18.4%, HR 0.58 (95% CI 0.47–0.70) Hyperkalemia: 2.5% vs. 1.9% ($p = .29$)
EPHESUS	R, P, DB, PC	6,632	≤40% (33%)	NR	Eplerenone 25 mg PO daily (increased to 50 mg PO daily if K ≤5.5 mmol/L after 4 weeks)	16 mo (median)	All-cause mortality: 14.4% vs. 16.7%, RR 0.85 (95% CI 0.75–0.96) CV death: 12.3% vs. 14.6%, RR 0.83 (95% CI 0.72–0.94) All-cause hospitalization: 45.0% vs. 46.1%, RR 0.95 (95% CI 0.89–1.02) HF hospitalization: 10.4% vs. 11.8%, RR 0.85 (95% CI 0.74–0.99) Hyperkalemia: 5.5% vs. 3.9% ($p = .002$)
RALES	R, P, DB, PC	1,663	≤35% (26%)	III and IV	Spironolactone 25 mg PO daily (increased to 50 mg PO daily if patient showed signs/symptoms of HF progression without evidence of hyperkalemia at 8 weeks)	24 mo (mean)	All-cause mortality: 34.5% vs. 45.9%, RR 0.70 (95% CI 0.60–0.82) CV death: 27.5% vs. 37.3%, RR 0.69 (95% CI 0.58–0.82) HF hospitalization: 26.2% vs. 35.7%, RR 0.65 (95% CI 0.54–0.77) Serious hyperkalemia: 2% vs. 1% ($p = .42$)

CV = cardiovascular; DB = double blind; HF = heart failure; HR = hazard ratio; K = potassium; LVEF = left ventricular ejection fraction; N = study population; NR = not reported; NYHA = New York Heart Association; P = prospective; PC = placebo controlled; PO = by mouth; R = randomized.

were also enrolled if their LVEF was 30–35% and their QRS interval was >130 ms (though this accounted for only 3.5% of the total enrolment). Patients were required to take an ACE inhibitor or angiotensin receptor blocker (ARB) and β-blocker and had to have been hospitalized for HF in the preceding six months. The inclusion criteria were extended to encompass patients who had not been hospitalized in the previous 6 months but who had an elevated B-type natriuretic peptide (BNP) (>250 pg/mL) or N-terminal pro B-type natriuretic peptide (NT-proBNP) level (>500 pg/mL for men and >750 pg/mL for women); these patients constituted 14% of the total enrolment. Excluded were patients with advanced renal dysfunction (estimated glomerular filtration rate <30 mL/min), hyperkalemia (>5.0 mmol/L), more-severe HF symptoms (NYHA class III–IV), or recent acute MI. The primary outcome was a composite of CV death or HF hospitalization. Secondary outcomes included the individual components of the primary outcome, death from any cause, hospitalization for any cause, and a composite of HF hospitalization or death from any cause.

The trial enrolled 2,737 patients with a mean age of 69 years and an LVEF of 26%. Seventy-eight percent were male, and the primary cause of HF was ischemia (69%). The majority of patients were receiving optimal medical therapy at baseline (94% on ACE inhibitor/ARB, 87% on β-blocker, and 85% on diuretic). Baseline rates of device therapy were low

(only 19% of patients had an implantable cardioverter defibrillator), and 8% were receiving cardiac resynchronization therapy. The study was stopped early, with a median 21-month follow-up, secondary to overwhelming benefit. A significant improvement in the primary outcome was observed with eplerenone (18.3% vs. 25.9%; ARR 7.6%; HR 0.63 [95% CI 0.54–0.74]). All other secondary outcomes demonstrated benefit, including death from any cause (ARR 3%; HR 0.76 [95% CI 0.62–0.93]). As expected, the rate of hyperkalemia (>5.5 mmol/L) was higher with eplerenone as compared with placebo (11.8% vs. 7.2%, p <.001) but was not different than placebo for serious hyperkalemia (>6.0 mmol/L) (2.5% vs. 1.9%, p = .29). This was expected, as the dosing protocol mandated a reduction in the study drug when the serum potassium level was ≥5.5 mmol/L. Other adverse events (such as hypotension, renal failure, and gynecomastia) did not differ between groups.

Overall, EMPHASIS-HF demonstrated a significant benefit with eplerenone for reducing CV death and HF hospitalization for patients with structurally poor hearts, good medication management, and mild symptoms. This benefit extended to all secondary outcomes, including a 3% absolute reduction in death from any cause despite other mortality-reducing medications, which corresponds to a "number needed to treat" of 34. However, it should be noted that patients with poor renal function or hyperkalemia were excluded, and the use of device therapy at baseline was low. Nonetheless, few recent HF trials have indicated this degree of benefit on top of established pharmacologic therapy.

Application in Practice

When applying the results of the aldosterone antagonist trials in practice, one must examine a few key therapeutic factors. All studies demonstrated a consistent benefit of aldosterone antagonism for patients with left ventricular (LV) systolic dysfunction. With the publication of EMPHASIS-HF results, the target HF population now includes patients with NYHA class II symptoms. When an aldosterone antagonist is considered in practice, it should be noted that the patients in EMPHASIS-HF, though not severely symptomatic, were at high risk of adverse CV events because their mean LVEF was markedly reduced, and most patients had had recent HF-related hospitalization. Additionally, the overall mortality rates were much higher in RALES (35% vs. 46%) than in EMPHASIS-HF (13% vs. 16%).

Aldosterone antagonists for HF have been underutilized. A large American cohort analysis indicated that aldosterone antagonists were used in only 34% of indicated HF patients, although the data did not account for those patients considered to be at high risk for hyperkalemia or renal dysfunction.[8] However, likely the most important therapeutic question is not whether to use an aldosterone antagonist in patients with symptomatic systolic HF but rather which one to use. In RALES and EMPHASIS-HF, both spironolactone and eplerenone reduced all-cause mortality by a similar degree (30% [ARR 11%] and 25% [ARR 3%], respectively). It would not be unreasonable to consider that the reduction in all-cause mortality in RALES would have been mitigated by increased use of β-blockers. This, however, provides evidence for the incremental beneficial effect of these agents on "ideal" medical management. From an efficacy standpoint, it appears as though the benefit of aldosterone antagonism is a class effect. Therefore, the most important factors to consider when deciding between spironolactone and eplerenone are adverse effects, drug interactions, and cost. With respect to hyperkalemia (>6.0 mmol/L), the rates were similar in RALES and EMPHASIS-HF (2.0% and 2.5%, respectively). The comparative advantage of eplerenone is its lower propensity to cause gynecomastia, which was similar to that of placebo in both EPHESUS and EMPHASIS-HF. In terms of drug interactions, eplerenone should not be used concurrently with strong CYP3A4 inhibitors and should be used cautiously with moderate CYP3A4 inhibitors. The most important factor from a patient's perspective is likely cost, which is approximately $0.25 per day for spironolactone versus approximately $3.00 per day for eplerenone (for a 25 mg dose). Because of the results of EPHESUS, the Common Drug Review did not recommend that eplerenone be covered by provincial drug plans. The bottom line is that eplerenone, despite having fewer unfavourable sex-related effects (gynecomastia, impotence), appears to have efficacy similar to that of spironolactone but is considerably more expensive than spironolactone.

When an aldosterone antagonist is used in practice, it is imperative that appropriate monitoring be used to minimize the risk of hyperkalemia and renal dysfunction. Serum potassium and creatinine should be checked at days 3 and 7 after an aldosterone antagonist is initiated, then once a month for 3 months and at least once every 3 months thereafter.[9] As most HF patients are receiving an ACE inhibitor and/or an ARB, the risk of hyperkalemia is increased. After the RALES results were released, a Canadian population-based cohort showed a threefold increase in hospitalizations for hyperkalemia that corresponded to a fourfold increase in prescriptions for spironolactone during the preceding 2 years.[10] Additionally, hyperkalemia-associated mortality increased from 0.3 to 2.0 per 1,000 patients. Therefore, patients with HF who are being considered for aldosterone antagonist therapy should be selected appropriately according to the inclusion criteria of the published trials (as opposed to treating all patients). The potential risks must be weighed carefully against the potential benefits, particularly in those with renal dysfunction or who are at risk of hyperkalemia, and all patients should be monitored closely according to recommended guidelines.

The success of the HF aldosterone antagonist study trifecta has spawned further studies, and sequels IV, V, and VI are poised to be completed in the next few years. Both the ALBATROSS and REMINDER trials are designed to investigate spironolactone and eplerenone, respectively, versus placebo in patients after an acute MI (24 to 72 hours).[11,12] Additionally, the TOPCAT trial is currently investigating spironolactone compared to placebo in patients with HF and preserved systolic function.[13]

Conclusion

The use of aldosterone antagonists for the treatment of HF dates back to the 1960s, when spironolactone in patients with refractory symptoms was initially studied with mixed results likely due to adverse drug reactions from the high doses used. Subsequently, the progression of this therapy in HF has been protracted; the results of the first large-scale trial (RALES) were published almost 40 years later. Spironolactone remained unaccompanied in the HF therapeutic armamentarium until the introduction of eplerenone, which demonstrated a reduction in death from any cause compared to placebo for both patients with post-MI LV systolic dysfunction and patients with class II systolic HF. In HF, however, aldosterone antagonists should be used judiciously in appropriately

selected patients, and close monitoring is warranted. The potential benefits must be weighed carefully against the possible harms (in particular, hyperkalemia and renal dysfunction). An important question remains as to which aldosterone antagonist to use in practice. Both have resulted in reduced mortality in patients with systolic HF by a similar degree. Though eplerenone has fewer sex-related adverse effects, it is considerably more expensive and may not be covered by provincial or private drug insurance plans. As the prevalence of HF increases and treatment evolves, we are likely to see even more sequels involving the established cast and bright newcomers of aldosterone antagonists, all looking to make their mark. Their future in the treatment of HF looks bright. The trilogy of trials of aldosterone antagonists in HF deserves more sequels, which is more than can be said for some to-remain-unnamed movie franchises.

References

1. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. New Engl J Med 1999;341:709–17.
2. Bayley TA, Forbath PG, Wilson JK, et al. Metabolic studies on patients with resistant heart failure treated by spironolactone. CMAJ 1962;87:1263–6.
3. Carruthers BM, Ledray RD, Seraglia M, et al. Effect of an aldosterone antagonist (spironolactone) on patients with severe congestive heart failure. CMAJ 1963;89:633–41.
4. Barnes BJ, Howard PA. Eplerenone: a selective aldosterone receptor antagonist for patients with heart failure. Ann Pharmacother 2005;39:68–76.
5. Pfizer Canada Inc. Inspra product monograph. http://www.pfizer.ca/en/our_products/products/monograph/172. Accessed August 8, 2011.
6. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. New Engl J Med 2003;348:1309–21.
7. Zannad F, McMurray JV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. New Engl J Med 2011;364:11–21.
8. Albert NM, Yancy CW, Liang L, et al. Use of aldosterone antagonists in heart failure. JAMA 2009;302(15):1658–65.
9. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;53:e1–90.
10. Juurlink DN, Mamdani MM, Less DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. New Engl J Med 2004;351:543–51.
11. Beygui F, Vicaut E, Ecollan P, et al. Rationale for an early aldosterone blockade in acute myocardial infarction and design of the ALBATROSS trial. Am Heart J 2010;160:642–8.
12. Impact of eplerenone on cardiovascular outcomes in patients post myocardial infarction (REMINDER). http://www.clinicaltrials.gov/ct2/show/NCT01176968?term=reminder+eplerenone&rank=1. Accessed August 4, 2011.
13. Aldosterone antagonist therapy for adults with heart failure and preserved systolic function (TOPCAT). http://www.clinicaltrials.gov/ct2/show/NCT00094302?term=topcat&rank=1. Accessed August 4, 2011.

CSIM News

Edmonton Physician Receives Honour from Mayo Clinic

Dr. Ann Colbourne recognized for outstanding contributions to internal medicine

University of Alberta Hospital physician Dr. Ann Colbourne has been selected by the Mayo Clinic as the latest recipient of its Plummer Society Award for Excellence. The division chief of general internal medicine in the Edmonton Zone of Alberta Health Services (AHS) is being honoured for her outstanding and unique contributions to practice, education, research, and administration in internal medicine.

Dr. Colbourne, whose, clinical passion is diabetes care with an emphasis on health promotion and disease prevention, is quick to point out the team effort behind this award, calling it a shared honour: "The amazing teams of health professionals I work with embody the real spirit of what the Plummer Society Award stands for."

Since 2007, the Mayo Clinic has presented a Plummer Society Award for Excellence every two years to a member of its alumni association who has demonstrated a commitment to the field of internal medicine and/or related subspecialties; demonstrated significant commitment to mentoring future generations of practitioners or scientists; achieved significant recognition in a chosen field of internal medicine or subspecialty; and is influential in that field and has contributed to the science in that field.

Dr. Colbourne – the third recipient of the award and first Canadian physician to receive it – currently leads an initiative that uses e-technology to deliver health services, expertise, and information to insulin pump patients in Newfoundland. By doing so, she is improving access and eliminating barriers to care across Alberta and beyond.

"We are indeed proud of Dr. Colbourne for her determination in pursuit of administrative and clinical excellence, and also for her tireless commitment to AHS," says Dr. Chris Eagle, AHS president and chief executive officer. "I know her patients adore her and rely on her expertise, as do her staff and colleagues."

The Plummer Society was founded in honour of Dr. Henry S. Plummer, one of Mayo's first physicians. Mayo Clinic is a nonprofit worldwide leader in medical care, research and education for people from all walks of life.

IN THE RELIABLE NOVOPEN®4

EFFECTIVE GLYCEMIC CONTROL[1]

EXCELLENT WEIGHT PROFILE DEMONSTRATED[3‡]

Mean weight change at 26 weeks with Levemir® vs. NPH: 0.4 kg vs. 1.9 kg; $p \leq 0.0001$

LOW INCIDENCE OF NOCTURNAL HYPOS DEMONSTRATED[2†*]

Incidence of events with Levemir® vs. NPH: 19 vs. 47; $p=0.031$. Similar overall hypoglycemia and A1C reduction for Levemir®, NPH, and glargine

ONCE-DAILY DOSING[1]

Covered on private plans, ODB, RAMQ & SK

There are plenty of reasons to start with Levemir®.

When starting a basal insulin, choose once-daily Levemir®.

Looking for more information to help get your patients started? Visit StartLevemir.ca for downloadable resources and sample requests.

Levemir® (insulin detemir) is indicated for the treatment of adult patients with type 1 or type 2 diabetes mellitus who require a long-acting (basal) insulin for the control of hyperglycemia.
Levemir® is also indicated for the treatment of pediatric patients with type 1 diabetes mellitus who require a long-acting (basal) insulin for the control of hyperglycemia. The safety and efficacy of Levemir® has not been studied in children below the age of 6 years.
Levemir® is also indicated for the treatment of type 2 diabetes mellitus in combination with oral anti-diabetic agents (OADs) [metformin or sulfonylureas] in adult patients who are not in adequate metabolic control on OADs alone. For safety reasons, the use of insulin in combination with thiazolidinedione is not indicated.
Levemir® also may be used in combination with short or rapid-acting mealtime insulin. As with all insulin preparations, hypoglycemic reaction, which is the most common adverse effect with insulin therapy, may be associated with the administration of Levemir®. Glucose monitoring is recommended for all patients with diabetes. Also, as with other insulins, patients may experience redness, swelling or itching at the site of injection. Levemir® should not be mixed with other insulins.

* Administered in the evening.

novo nordisk®

Novo Nordisk Canada Inc., 300-2680 Skymark Avenue, Mississauga, Ontario L4W 5L6.
Tel: (905) 629-4222 or 1-800-465-4334. www.novonordisk.ca

PAAB

Levemir® (insulin detemir)

See prescribing summary on page 162

A Father's Gift

Donald Farquhar MD

About the Author
Donald Farquhar practises internal medicine and respirology at St. Joseph's and University Hospitals, in London, Ontario, and teaches in the Schulich School of Medicine at the University of Western Ontario. Correspondence may be directed to Donald.Farquhar@sjhc.london.on.ca.

Of all the questions I am asked, on the job or off, during the month of December, the toughest to answer by far is, "What do you want for Christmas, Dad?" The truth is, I tell my two daughters there isn't anything I haven't been given already – and there isn't much in the material world that this old dad wants or needs. Well, maybe a new set of golf shoes, or a few pairs of socks to replace those whose mates always seem to go missing whenever dad does the laundry. Each year, predictably enough, that tired old response is greeted with exasperated sighs and rolling of the eyes.

Thirty Christmases ago my own father told me what John Leonard, the *New York Times* columnist, had written in an article entitled "Gifts." He answered his children's question "What do you want for Christmas?" with "I want you to listen to Beethoven's quartets instead of the Grateful Dead. I want to go to Mars. I want to be able to write like Leo Tolstoy, or at least like Russell Baker (a fellow *Times* columnist). I want Bobby Kennedy to be alive. I want to be your father."

As dad pointed out to me, what John Leonard described so clearly in his wish list was the wide range of human yearnings that surface at this time of year. The hope that others might open their senses to the beauty that we see and hear in the world around us. The desire to embark on a great adventure. The aspiration to be the best that we can be. The desire to recover something or someone we have lost. And the longing for a renewed connection with those we love the most.

A few years ago, I made a study of the life of the late Dr. Isaac (Ike) Taylor, a distinguished internist, scholar and physician-leader who served as dean of the School of Medicine at the University of North Carolina in the 1960s. Although Dr. Taylor was a transformative figure in the history of that institution, he is perhaps better known as the father of singer-songwriters James, Livingston, Kate, and Alex. James Taylor, in particular – the archetypal sensitive singer-songwriter and "professional autobiographer" of the 1970s – has written songs that constitute much of the "theme music" of my life and the lives of many of my fellow boomers.

But like others of his generation, James Taylor in his youth had fallen prey to the excesses of the '60s, and before long found himself addicted to heroin. One day, strung out, vulnerable, and alone in Greenwich Village in New York City, he made a rare telephone call home. From the sound of his voice, his father knew instinctively that he was in trouble. "Stay put," Ike said. "What's your address? I'll be right there." At that moment, Dr. Taylor dropped everything, flew to New York City, rented a station wagon, gathered up his son and some of his belongings, and drove south through the night until they were safe at home again.

Consumed by his work and career – and by his own personal demons – Dr. Taylor had become the prototypical absentee physician-parent. Long before, in the late 1950s, after being drafted into the Naval Medical Corps, he had served as medical officer to a military and scientific expedition to the South Pole. This kept him far from home and isolated from loved ones for almost two years. On his return, he was never quite able to reinsert himself into his family's life, remaining emotionally distant from his children and even from his wife, Trudy. But in mounting that daring overnight rescue mission – retrieving his son from a desperate situation and bringing him home – he was saying, simply, "I want to be your father."

Giving gifts and renewing the bonds between us are at the heart of many of the year-end festivals celebrated by the world's various cultural and faith communities. So too – whether it is Chanukah, Christmas, Diwali, Eid ul-Fitr, Kwanzaa, or Rohatsu that we observe – is the theme of light overcoming darkness, within and among us. We live in a world where too many know the darkness of poverty, hunger, illness, or despair. When we reach out to them – responding to that sometimes long-dormant human urge to nurture and protect – we are saying, "I want to be your father … or mother … or sister or brother … or friend." And in being present in that way, we can shed, beyond our own circle of family and friends, a little of the light that this season brings.

Wegener's Granulomatosis Causing Gastrointestinal Hemorrhage and Perforation of the Small Intestine: A Case Report and Review of the Literature

Monika Pawlowska MD, Eric M. Yoshida MD, David Collins MD, Edward Jones MD

About the Authors
Monika Pawlowska is a fellow in endocrinology, Eric Yoshida is a staff gastroenterologist, David Collins is a staff rheumatologist, and Edward Jones a staff pathologist, all with the University of British Columbia, in Vancouver, British Columbia. Correspondence may be directed to eric.yoshida@vch.ca.

Wegener's granulomatosis (WG) is a small-vessel vasculitis that typically affects the upper and lower respiratory tracts and the kidneys. Although the disease may affect any organ, gastrointestinal involvement is exceedingly rare. There are very few previously reported cases of histologically confirmed WG-induced gastrointestinal perforation or hemorrhage.[1–11] We herein describe only the second case of WG to cause *both* perforation and hemorrhage.

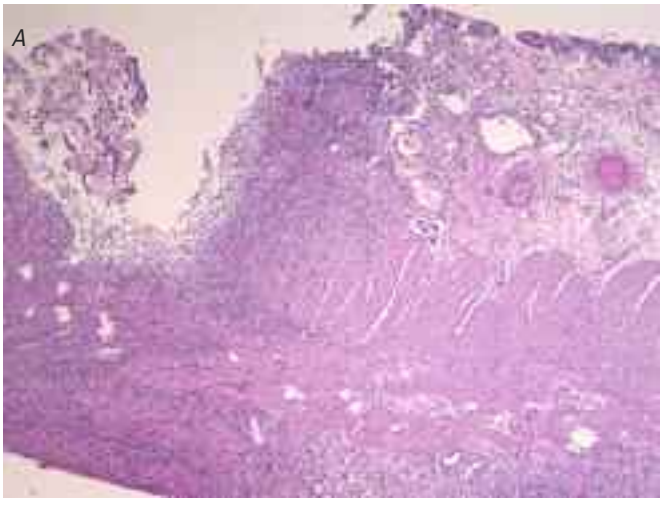
Case Report

A previously healthy, 58-year-old man, presented with hoarseness, hearing loss, exertional dyspnea, non-productive cough, fatigue, and a 10 kg weight loss. Laryngoscopy showed left vocal cord paralysis. A computed tomography (CT) scan revealed a left-sided nasopharyngeal mass, and a large apical lung mass, concerning for malignancy. Bronchoscopy was negative for malignancy, CT-guided fine-needle aspiration (FNA) was nondiagnostic, and a video-assisted thoracoscopic lung biopsy was planned. However, as part of the workup, ANCA serology was sent; it came back positive (1:640) with PR3 of 139 units, and Wegener's granulomatosis was suspected. Remaining laboratory investigations showed an erythrocyte sedimentation rate (ESR) of 90 mm/h, a C-reactive protein (CRP) level of 186 mg/L, a white blood cell count of 10.7 giga/L, hemoglobin at 88 g/L, and platelets at 665 giga/L. Electrolytes, renal function (Cr 81 μmol/L), and urinalysis were normal.

Since there was no evidence of deteriorating organ function, steroids and cyclophosphamide were deferred. However, before tissue to confirm the diagnosis was obtained, the patient developed an incomplete small bowel obstruction at the level of the distal ileum, visualized on CT scan. Despite nasogastric decompression, peritonitis developed. Laparotomy showed two terminal ileum perforations with small, patchy areas of necrosis throughout the small bowel. At this point, only one dose of intravenous (IV) methylprednisolone had been administered. Five subsequent surgeries were necessary, with resection of over 1 m of small bowel. Perioperatively, broad spectrum antibiotics were administered.

Pathologic examination of the resected specimen showed segmental ulceration and transmural necrosis of small bowel (Figure 1). The deep mucosal ulcerations had active inflammation, scattered giant cells, and eosinophils but no well-formed granulomas. Within the ulcerated mucosa and adjacent submucosa, arteries had the appearance of leukocytoclastic vasculitis. These findings were compatible with WG of the small bowel.

As there was no immediate benefit to starting cyclophosphamide, this was deferred to prevent overwhelming sepsis; however, steroid treatment was continued. Two days following his last surgery, the patient developed severe



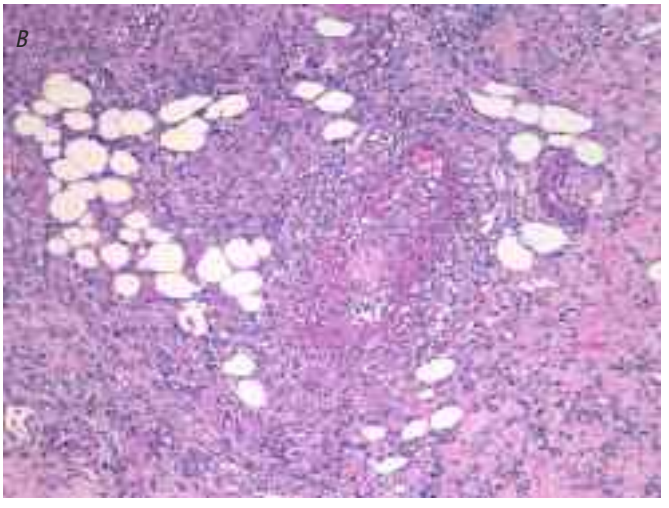


Figure 1. *A*, Small bowel with perforating ulceration and inflammation. The adjacent mucosa shows sloughing with submucosal congestion and edema consistent with ischemic damage. *B*, Fibrinoid leukocytoclastic vasculitis of submucosal vessel.

Table 1. Previously Reported Cases WG Causing Gastrointestinal Perforation or Hemorrhage

Patient	Location	Pulmonary or Renal Disease	Pathology	Need for Surgery	Medical Treatment[§]	Outcome
Intestinal Perforation						
37-M (3)	Ileum	Both	Vasculitis	Yes	S + C	Survival
26-M (4)	Sigmoid	Both	Vasculitis	Yes	C	Survival
69-M (5)	Jejunum	Both	Vasculitis	Yes	S + C	Death from RF
46-F (6)	Colon	Pulmonary	Vasculitis	Yes	S	Death from GI cause
44-F (7)	Ileum	Neither	Vasculitis	Yes	S + C	Survival
44-M (8)	Ileum	Pulmonary	Vasculitis	Yes	S	Survival
Bleeding Ulcerations						
46-M (9)	Ileum	Both	Vasculitis	Yes	S + C	Survival
46-M (10)	Jejunum	Renal	Vasculitis	Yes	S + C + IVIG	Survival
30-M (11)	Colon	Both	Granuloma and giant cells	No	S + C	Survival
34-M (12)	Esophagus, stomach, duodenum*, jejunum*, colon*	Renal	Vasculitis	Yes[†]	S + C	Survival
Both						
54-F (13)	Ileum, colon	Renal	Vasculitis	Yes[†]	S + C	Survival

C = cyclophosphamide; GI = gastrointestinal; RF = renal failure; S = steroids; WG = Wegener's granulomatosis.

*Denotes site of *bleeding* ulcer when multiple ulcerations present.

[†]Also required arterial embolization.

[§]Medical treatment prescribed/continued following gastrointestinal event.

gastrointestinal hemorrhage from three pre-pyloric ulcers. These ulcers had to be surgically oversewn. Bleeding continued, and repeat endoscopy done 3 days later showed several new duodenal ulcers.

Because of disease progression, IV cyclophosphamide (650 mg) was started and intravenous immune globulin (IVIG) was administered. Despite this, brisk bleeding recurred, with a fall in hemoglobin to 38 g/L. Endoscopy showed frank arterial bleeding from a visible vessel in the duodenum requiring urgent angiography and embolization.

IV cyclophosphamide (850 mg) was subsequently repeated and the patient stabilized on oral cyclophosphamide and prednisone. A year later, his Wegener's disease remains in remission, with no further gastrointestinal involvement. On repeat imaging, the nasopharyngeal and lung masses have resolved. Renal function remained normal throughout.

Discussion

Intestinal manifestations of Wegener's disease are limited to individual case reports. From the English medical literature, Table 1 summarizes 11 patients with histologically confirmed gastrointestinal WG causing intestinal perforation,[1–6] gastrointestinal hemorrhage,[7–10] or both.[11] This is only the second instance of both intestinal perforation and gastrointestinal bleeding presenting in the same patient.

Of the 11 patients reviewed, six had pulmonary and seven had renal involvement prior to onset of gastrointestinal disease. One patient had small bowel WG without renal or pulmonary disease,[5] and another developed deteriorating kidney function and cavitating pulmonary lesion after bowel perforation.[3] Gastrointestinal involvement usually appeared early in the disease course, with eight patients experiencing systemic symptoms for less than 3 months prior to their abdominal event (range 5 days–24 months).

Three patients *presented* with abdominal pain[3,4,10] and one with bloody diarrhea[9] while not taking immunosuppressants. In two cases, this progressed to intestinal perforation and severe lower gastrointestinal hemorrhage[3,9] prior to initiation of therapy. In the remaining cases, intestinal perforations developed,[4] and upper gastrointestinal bleeding[10] developed shortly after initiation of steroids. Six patients who did *not* have abdominal complaints at presentation to hospital, developed complications of gastrointestinal WG shortly after initiation of immunosuppressive therapy for another indication (range 1–12 days). In one instance, the patient was treated with oral prednisolone and IV cyclophosphamide for a full year prior to abdominal complications.[2] In one case, the duration of preceding medical therapy was not clear.[6]

Although the route of administration was not always specified, cyclophosphamide and corticosteroids were either initiated or continued following gastrointestinal perforation and/or hemorrhage in nine of 11 patients.[1–3,5,7–11] In two of these cases,[8,9] persistent gastrointestinal bleeding subsided with a change of cyclophosphamide from an oral to intravenous formulation. One patient sustained remission on oral prednisone alone.[6] Although surgical/radiological intervention was required in the vast majority (see Table 1), nine patients survived without further gastrointestinal complications and only one patient died of gastrointestinal complications.[4]

In our case, histopathology supports small bowel WG but, to prevent further bleeding, gastric and duodenal ulcers were not biopsied. The rapid development of multiple new ulcers on previously documented normal mucosa would be atypical for either stress ulcers or peptic ulcer disease, especially in the setting of treatment with a pantoprazole infusion. Although the patient had received corticosteroids, a large meta-analysis[12] showed that corticosteroid therapy was not associated with increased rates of peptic ulcers. As such, we are confident these ulcerations were caused by vasculitis.

The fact that the ulcers have not recurred following remission of WG also suggests an etiologic role.

Previous case reports have suggested immunosuppressive therapy may cause or exacerbate gastrointestinal complications.[4,10] In the case of our patient, abdominal symptoms with CT evidence of terminal ileum inflammation developed prior to any such therapy and only a single dose of IV methylprednisolone was given prior to the development of peritonitis. This chronology does not implicate corticosteroids as a causative agent for intestinal perforation. In fact, the steroid treatment may have prevented the gastroduodenal ulcers from necrosing and perforating, as they did in the small bowel.

In our experience, the intestinal vasculitis was very difficult to control medically. Steroid therapy alone was not sufficient to prevent further ischemia and, therefore, 2 days of IVIG was administered. IVIG was employed once previously by Chow et al., to control WG-induced gastrointestinal bleeding.[8] In our patient, arterial embolization was ultimately needed to control the gastrointestinal haemorrhage, and the combination of medical therapy prevented further intestinal events. Although it is difficult to discern just how much the IVIG contributed to this success, its use as a bridging agent seemed reasonable given the delay in using cytotoxic agents.

This case, and others before it, demonstrates that even though WG does not typically affect the gastrointestinal tract, abdominal symptoms in a patient with known or suspected WG should be taken very seriously. Perhaps if immunosuppressive therapy had been commenced sooner in our patient, the intestinal tract complications might not have occurred.

References

1. Tokuda M, Kurata N, Daikuhara J, et al. Small intestinal perforation in Wegener's granulomatosis. J Rheumatol 1989;16:547–9.
2. Storesund B, Gran JT, Koldingsnes W. Severe intestinal involvement in Wegener's granulomatosis: report of two cases and review of the literature. Br J Rheumatol 1998;37:387–90.
3. Skaife P, Lee S, Maitra D, et al. Intestinal perforation as a presentation of Wegener's granulomatosis. Hosp Med 2000;61:286–7.
4. Huisman AM, van der Meulen MF, Raaymakers TWM, et al. Subacute painful quadriplegia and purpura. Ann Intern Med 2003;139:1048–9.
5. Shaikh FM, Sabu CB, Peirce TH, et al. Extensive intestinal ischaemic necrosis in Wegener's granulomatosis. Gut 2006;55:1368–9.
6. Deniz K, Ozseker S, Balas S, et al. Intestinal involvement in Wegener's granulomatosis. J Gastrointestin Liver Dis 2007;16:329–31.
7. Coward RA, Gibbons CP, Brown CB, et al. Gastrointestinal haemorrhage complicating Wegener's granulomatosis. Br Med J 1985;291:865–6.
8. Chow FYF, Hooke D, Kerr P. Severe intestinal involvement in Wegener's granulomatosis. J Gastroenterol Hepatol 2003;18:749–50.
9. Kuwahara Y, Shima Y, Tanaka T, et al. Successful treatment with intravenous cyclophosphamide pulse therapy of severe intestinal involvement in Wegener's granulomatosis. Scand J Rheumatol 2006;35:243–5.
10. Deger SM, Sahin T, Vural C, et al. Wegener's granulomatosis with massive gastrointestinal hemorrhage due to jejuna and colonic involvement: report of a case. Surg Today 2008;38:166–9.
11. Strivens RL, Bateman A, Arden NK, et al. Intestinal perforation and jejuna haemorrhage due to Wegener's granulomatosis. Clin Exp Rheumatol 2005;23:124.
12. Conn HO, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med 1994;236:619–32.

Giant Cell Arteritis

Sankalp V. Bhavsar MD

About the Authors
Sankalp Bhavsar is a 3rd-year internal medicine resident at the University of Calgary, in Calgary, Alberta. Correspondence may be directed to sankalp.bhavsar@gmail.com.

Introduction and Epidemiology

Giant cell arteritis (GCA) is a vasculitis affecting large and medium-sized arteries, especially the cranial branches of the aortic arch. Although the disease is also referred to as temporal arteritis, the vasculitis is not limited to the temporal arteries, and, therefore, GCA is a more appropriate term.

The incidence of GCA increases with age and is a disease mostly seen in patients greater than 50 years of age. Women are affected approximately three times more often than men. Individuals of Northern European origin, particularly those of Scandinavian descent, are at highest risk with annual incidence rates of exceeding 20 cases per 100,000 people. Incidence rates of GCA are lower in Asian, African American, and Hispanic populations.[1]

Pathogenesis

The etiology of GCA is unknown; however, it is likely that both genetic and environmental factors contribute to the development of the disease. A familial aggregation of GCA has been observed, and there is a genetic association between GCA and the HLA-DRB1*04 alleles. It has been suggested that GCA has an infectious etiology, especially given the observation of fluctuating annual and seasonal incidences, but evidence to support this claim is lacking. A history of cigarette smoking seems to be associated with an increased risk of GCA in women.[1,2]

Pathological specimens show a panarteritis with mononuclear infiltrates in all layers of the arterial wall. T-cells and macrophages, and sometimes multinucleated giant cells, are present. T-cell-mediated processes are important in the pathogenesis of GCA, and the CD4+ T cell plays a key role in the development of vasculitic lesions. The antigen-presenting dendritic cells present in medium-sized arteries may be responsible in activating T cells, but the antigens recognized by CD4+ T cells remain unknown. Cytokines are also important in causing the inflammatory response.[3]

Clinical Features

Systemic complaints such as fever, fatigue, anorexia, and weight loss are common, and present in most patients. Fevers are usually low grade but can be up to 39–40°C in 15% of patients and may be the only manifestation of GCA. A new-onset of headache is reported by approximately two-thirds of patients with GCA. Although the classic headache is located over the temporal regions, the headache can involve any part of the head. Almost one-half of patients have jaw claudication as a result of ischemia of the muscles of mastication.[4] Jaw claudication is also the symptom with the highest predictive value of a diagnosis of GCA.[5]

Up to 20% of patients can suffer permanent partial or complete visual loss in one or both eyes, one of the most feared complications of GCA. Visual loss is usually due to anterior ischemic optic neuropathy (AION). AION usually begins unilaterally, but there is a significant risk to the other eye within 1–2 weeks if treatment is not initiated. Amaurosis fugax, a transient monocular loss of vision, may herald a more permanent visual loss for some. Transient diplopia occurs in less than 10% of patients.[4]

There is a close association of GCA with polymyalgia rheumatica (PMR). Patients with PMR typically have pain and morning stiffness in the shoulder and pelvic girdles and neck. Similar to GCA, PMR is more common in individuals over 50 years of age, has a female predisposition, is characterized by substantial increases in acute-phase reactants, and responds rapidly to glucocorticoids. About 40–60% of patients with GCA have PMR; in contrast, approximately 20% of patients with PMR have GCA. The manifestations of PMR may precede, occur simultaneously, or develop after the appearance of GCA. Interestingly, a minority of patients with PMR without clinical features suggesting GCA have positive temporal artery biopsies.[1,4]

Less common clinical features of GCA include arm claudication in up to 15% of patients due to involvement of the subclavian, axillary, and brachial arteries. Involvement of the aorta can lead to thoracic aortic aneurysms as well as dissection. These complications generally occur several years after the initial diagnosis of GCA. Neurologic manifestations, such as neuropathy, can be seen in about 30% of patients. The incidence of transient ischemic attacks (TIAs) or strokes due to obstruction or occlusion of the internal carotid or vertebral arteries is less than 5%, and it is very rare for GCA to cause inflammation in the intracranial or intradural arteries. Respiratory symptoms, such as cough, sore throat, and hoarseness are present in approximately 10% of GCA patients.[4]

Physical examination may reveal abnormalities of the temporal artery. A beaded, prominent, or enlarged temporal artery is most predictive finding to support this diagnosis.[5] The temporal artery pulse may be absent or there may be tenderness to palpation of the artery. About half of GCA patients will have scalp tenderness. In patients with acute visual loss from anterior ischemic optic neuropathy, the optic disc may be swollen with blurring of the disc margins, and small hemorrhages may be seen. Over time, the optic disc atrophies, and a pale disc is seen. About 25% of GCA patients have peripheral arthritis and edema. With GCA involvement of the aortic arch, bruits may be heard over the carotid, subclavian, axillary, and brachial arteries, and pulses may be decreased or absent in the arms or neck.[4]

Diagnosis

Laboratory tests are non-specific for diagnosing GCA. An elevated erythrocyte sedimentation rate (ESR) of 40 mm/hr or more is seen in most GCA patients, but a normal ESR can be seen in approximately 4% of patients. C-reactive protein (CRP) may be a more sensitive marker than the ESR for GCA. A moderate normochromic, normocytic anemia is also common.

Table 1. 1990 American College of Rheumatology Classification Criteria for Giant Cell Arteritis*

Age of disease onset (development of signs or symptoms) at age 50 or older
New headache or new localized pain in the head
Temporal artery tenderness or decreased pulsation (unrelated to arteriosclerosis of cervical arteries)
Elevated erythrocyte sedimentation rate ≥50 mm/h (by Westergren method)
Abnormal artery biopsy (showing vasculitis with a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells)

*A patient is said to have giant cell arteritis if at least 3 of these 5 criteria are present; this yields a sensitivity of 94% and a specificity of 91%.

Other laboratory abnormalities can include leukocytosis, thrombocytosis, and raised alkaline phosphatase (ALP).[5,6]

Imaging, including ultrasonography, magnetic resonance imaging/angiography (MRI/MRA), and positron emission tomography (PET) can also be helpful. However, these studies are not routinely performed. An annual chest radiograph is sufficient to screen for a thoracic aortic aneurysm.[4]

The gold standard to diagnose GCA is a temporal artery biopsy and should be done in all patients suspected to have the diagnosis. A temporal artery biopsy should be performed as soon as possible, and the biopsy length should be at least 1 cm. The temporal arteries are biopsied in GCA due to their easy accessibility – not due to these arteries being the focus of GCA. Temporal artery biopsies can occasionally be falsely negative. Possible reasons for false negative biopsies include sampling error to due to the presence of skip lesions with GCA and obtaining too short a sample length. The decision whether to routinely perform bilateral or unilateral temporal artery biopsies remains somewhat controversial. A unilateral temporal artery biopsy is sufficient in most cases to diagnose GCA. Bilateral biopsies should be considered in those with a high suspicion of disease.[7,8]

The American College of Rheumatology (ACR) formed classification criteria for GCA in 1990. A patient is said to have GCA if at least three of five criteria are present (Table 1). The presence of three or more criteria yields a sensitivity of 94% and a specificity of 91%.[9]

Treatment

Treatment should be started immediately when the diagnosis of GCA is strongly suspected. Treatment of choice is high-dose glucocorticoids. Importantly, since the positivity rate of temporal artery biopsies is unaffected by treatment with glucocorticoids,[10] treatment should not be delayed until a biopsy is performed. The initial dose of prednisone is usually 40–60 mg daily. This dose should be continued for two to four weeks until reversible signs and symptoms of disease have resolved and acute-phase reactants have normalized. Initial high-dose intravenous glucocorticoids can be used in patients with recent visual loss, but the benefit of this approach is unclear.[4,7] Steroids are usually tapered after the initial two to four weeks of high-dose treatment. Tapering should be done gradually to prevent a relapse of disease.

The duration of glucocorticoid treatment is quite variable but can usually be discontinued in 1–2 years. Patients should receive adequate osteoporosis prophylaxis with calcium and vitamin D. A baseline bone-mineral density (BMD) test should be obtained, and patients with a low BMD should be started on a bisphosphonate.[4]

The addition of methotrexate as a steroid-sparing agent can be considered, especially in those at high risk of adverse effects from glucocorticoids.[4,7] The adjunctive use of methotrexate was shown to lower the relapse rate as well as cumulative exposure to glucocorticoids in a meta-analysis of three randomised controlled trials.[11] The use of other immunosuppresants, such as azathioprine and antitumor necrosis factor α (anti-TNFα) drugs, has not shown to be beneficial.[4] Low-dose aspirin was associated with a lower rate of visual loss and cerebral ischemic strokes in retrospective studies.[12] The use of low-dose aspirin is, therefore, recommended in all patients without contraindications in conjunction with a proton-pump inhibitor due to combined treatment with glucocorticoids.[4,7]

References

1. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum 2009;61:1454–61.
2. Richards BL, March L, Gabriel SE. Epidemiology of large-vessel vasculidities. Best Pract Res Clin Rheumatol 2010;24:871–83.
3. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. N Engl J Med 2003;349:160–9.
4. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet 2008;372:234–45.
5. Smetana GW, Shmerling RH. Does this patient have temporal arteritis? JAMA 2002;287:92–101.
6. Gonzalez-Gay MA, Lopez-Diaz MJ, Barros S, et al. Giant cell arteritis: laboratory tests at the time of diagnosis in a series of 240 patients. Medicine (Baltimore) 2005;84:277–90.
7. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2009;68:318–23.
8. Boyev LR, Miller NR, Green WR. Efficacy of unilateral versus bilateral temporal artery biopsies for the diagnosis of giant cell arteritis. Am J Ophthalmol 1999;128:211–5.
9. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122–8.
10. Achkar AA, Lie JT, Hunder GG, et al. How does previous corticosteroid treatment affect the biopsy findings in giant cell (temporal) arteritis? Ann Intern Med 1994;120:987–92.
11. Mahr AD, Jover JA, Spiera RF, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. Arthritis Rheum 2007;56:2789–97.
12. Lee MS, Smith SD, Galor A, et al. Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. Arthritis Rheum 2006;54:3306–9.

Q Fever: A Rare Cause of Community-Acquired Pneumonia?

Stephen Pizzale MD, Cheryl Main MD, Atreyi Mukherji MD

About the Authors
Stephen Pizzale (right) is a 3rd-year internal medicine resident, Cheryl Main is an associate professor in infectious diseases and medical microbiology, and Atreyi Mukherji is an associate professor in infectious diseases, all with McMaster University, in Hamilton, Ontario. Correspondence may be directed to stephen.pizzale@medportal.ca.

Case Report

A 66-year-old man presented to the emergency department complaining of fever, shortness of breath, and weakness. His medical history included hypertension, chronic obstructive pulmonary disease (COPD) secondary to a 70 pack-year smoking habit, chronic interstitial lung disease, gout, and chronic shoulder tendinitis. Two years ago, he had undergone quintuple coronary artery bypass graft (CABG).

Until this illness, he had been well, working as a self-employed furniture mover. His illness had evolved over a 3-week period. He noted progressive malaise, fevers, chills, and a worsening of his chronic non-productive cough. He had attended the emergency department 1 week into his illness and was told that he was suffering a viral illness. Fluids and non-steroidal anti-inflammatories were recommended. Despite this, his symptoms continued to worsen to the point where he could no longer cope at home and he returned to the emergency department. His vital signs in the ER were as follows: temperature 39.3°C, heart rate 107 beats per minute, blood pressure 85/53 mm Hg, respiratory rate 16 breaths per minute, and oxygen saturation on room air of 93%. The patient looked unwell.

Physical examination was remarkable for only for a mild respiratory wheeze. There were no cardiac murmurs and no meningeal signs. There was no obvious source of infection.

Laboratory investigations revealed a leukocyte count of 10.1 $\times 10^9$/L (absolute neutrophil count 8.4 $\times 10^9$/L). Other cell counts were normal. Electrolytes were normal, but the serum creatinine was elevated at 154 μmol/L. Arterial blood gas (on room air) revealed pH 7.34, P_{CO_2} 26 mm Hg, P_{O_2} 98 mm Hg, and bicarbonate 14 mmol/L. His lactate level was elevated at 3.2 mmol/L. Aspartate transaminase, alanine transaminase, and γ-glutamyltransferase were elevated at 38 U/L, 51 U/L, and 100 U/L, respectively, while alkaline phosphatase and total bilirubin remained normal.

The patient was fluid resuscitated with 6 L of intravenous crystalloid. Blood, urine, and sputum cultures were sent for testing, and he was started on piperacillin/tazobactam and vancomycin. His chest radiograph changed over a 24-hour period, with the appearance of bilateral interstitial reticular infiltrates (Figure 1). Urinalysis and blood cultures were negative. The patient was transferred to the Intensive Care Unit (ICU) for further resuscitation and respiratory support; however, the source of his infection remained a mystery.

Further enquiry revealed that he had travelled to a rural area along the St. Lawrence River several times in the 3–4 weeks before he fell ill. He made several trips to a trailer park as well as a farmhouse. He stated that he had no direct contact with animals; however, he did note that there were several feral cats that frequented the trailer park. He did not have any direct contact with them. He was not aware of any tick bites.

The Infectious Disease Service was consulted 2 days after his admission to assist in determining the source of the presumed infection. Serologies for Q fever, legionella, bartonella, toxoplasmosis, and blastomyces were requested.

The patient underwent bronchoscopy, and subsequently transesophageal echocardiography (TEE), with negative results. Blood cultures and human immunodeficiency virus serology were negative.

Approximately 10 days after admission, the Q fever serology was completed and antibody titres were as follows: phase II IgG 1:256, phase II IgM 1:256, phase I IgG <1:16, phase I IgM 1:128 – consistent with acute infection.

Doxycycline100 mg PO bid was started. With the addition of doxycycline, the patient improved clinically and was discharged home to complete a 21-day treatment course. He was well at a follow-up clinic 2 weeks later.

Discussion

Microbiology

Q fever is caused by *Coxiella burnetii*, and obligate intracellular gram-negative bacterium.[1] It is related to the *Legionella, Francisella,* and *Rickettsia* families of organisms.[1] It was first described by Edward

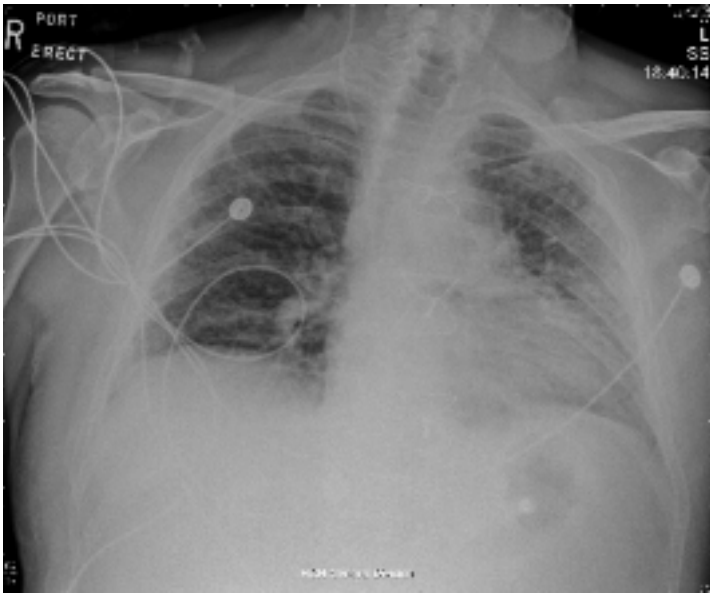


Figure 1. Chest radiograph taken 24 hours after admission showing bilateral interstitial reticular disease.

Holbrook Derrick in Australia in 1935 among febrile abattoir workers.[2] Clinically, Q fever can be divided into acute and chronic forms.[2,3] The two forms can be differentiated by serology. Antibodies to phase I represent chronic disease, and antibodies to phase II represent acute disease.[4]

Epidemiology

Q fever is a zoonosis that is found worldwide, with the exception of New Zealand. The reservoir includes wild and domestic mammals, birds, and also ticks. Domesticated livestock represent the most important source for human infection. Cats and dogs may also be reservoirs.[1,5]

Q fever is not a notifiable disease in many countries; therefore, the exact incidence is difficult to assess. In our region, it is a notifiable disease, and in Toronto, Ontario, there have been only seven confirmed cases over the past 10 years (1999–2009),[6] although one report lists it as a cause of 10% of community-acquired pneumonias in Nova Scotia.[2]

Since the risk of infection with Q fever is related to animal exposure, people at greatest risk include farmers, veterinarians, abattoir workers, and those in contact with dairy products as well as laboratory workers.[1,2,5,7] Infected animals shed the bacteria in their urine, feces, and milk and birth products. The primary mode of human infection is through the aerosol route. The bacteria frequently become aerosolized during the birthing process, and the organism has been documented to be spread by wind.[2] Person-to-person transmission is very rare and does not represent the majority of cases.

Clinical Features

The incubation period for acute Q fever ranges from 1 to 3 weeks depending on the inoculating dose. Most cases are asymptomatic or present as a non-specific illness. Acute Q fever has two classic presentations: pneumonia and granulomatous hepatitis.[5] The presentation varies based on geography. In Nova Scotia, the majority of cases are pneumonia, whereas in France, hepatitis predominates. It is hypothesized that the ingestion of raw milk may play a role in the development of the hepatitis.

Most cases of Q fever are mild and self-limited. In patients who do become symptomatic, the onset is usually abrupt, with acute onset of fever, chills, and headaches (typically retro-orbital). This can be associated with an atypical pneumonia-like picture; however, radiographically Q fever cannot be distinguished from other microbiological causes. There may be an associated bradycardia. Gastrointestinal symptoms such as nausea, diarrhea, and abdominal pain can also be seen. In one European study, only 10 of 1,261 cases required ICU admission.[2]

Chronic Q fever is defined by an illness lasting longer than 6 months. Q fever endocarditis is the predominant manifestation and can be fatal. Patients with underlying valvular disorders or chronic health conditions may be at increased risk of developing chronic Q fever. The recommendation is to follow up these patients with serology every 3 months.

Diagnosis

Most laboratories are unable to grow *C. burnetii* from culture. Isolation of the bacterium requires bio-safety level III due to its extreme infectivity. The diagnosis of Q fever is made with serology. A fourfold rise in antibody titre between acute and convalescent serum is considered diagnostic. Another sample should be drawn 2–4 weeks later.

Acute Q fever is characterized by antibodies to phase II antigens, whereas chronic Q fever is characterized by antibodies to phase I. When titres are drawn early, there are no detectable antibodies to *C. burnetii* (phase I and II titres <1:8). Titres drawn 2 weeks following symptom onset usually reveal phase II antibody titres of 1:128 or greater, while phase I titres are <1:8, indicating acute infection. In chronic Q fever, phase I antibodies titres can reach up to 1:16,384.[2]

Treatment

C. burnetii is resistant to beta-lactams and aminoglycosides. It is susceptible to rifampin, co-trimoxazole, and fluoroquinolones.[8] Once the diagnosis is made, the recommended treatment is doxycycline 100 mg bid for 10 days.[2] The treatment for chronic Q fever includes doxycycline and hydroxychloroquine treatment for months to years.

References

1. Maurin M, Raoult D. Q fever. Clin Microbiol Rev 1999;12(4):518–53.
2. Marrie TJ. Q fever pneumonia. Infect Dis Clin North Am 2010;24(1):27–41.
3. Gikas A, Kokkini S, Tsioutis C. Q fever: clinical manifestations and treatment. Expert Rev Anti Infect Ther 2010;8(5):529–39.
4. Kazar J. Immunity in Q fever. Acta Virol 1988;32(4):358–68.
5. Angelakis E, Raoult D. Q fever. Vet Microbiol 2010;140(3–4):297–309.
6. Toronto Public Health. Rare Reportable Communicable Diseases 2009. Toronto (ON): Toronto Public Health, 2009; http://www.toronto.ca/health/cdc/communicable_disease_surveillance/statistics_and_reports/annual_reports/pdf/2009/2009_rare_report.pdf.
7. Hartzell JD, Wood-Morris RN, Martinez LJ, Trotta RF. Q fever: epidemiology, diagnosis, and treatment. Mayo Clin Proc 2008;83(5):574–9.
8. Watanabe A, Takahashi H. Diagnosis and treatment of Q fever: attempts to clarify current problems in Japan. J Infect Chemother 2008;14(1):1–7.

Dr. Julian Derwent Loudon and Canada's First Electrocardiograph

Peter A. Kopplin MD

About the Author
Peter Kopplin practises general internal medicine at St. Michael's Hospital, in Toronto, Ontario. Correspondence may be directed to kopplinp@smh.ca.

Willem Einthoven was very human when it came to money. After developing his string electrocardiograph in 1901, he turned its commercial production over to a German company, Edelmann and Sons of Munich. When a disagreement over royalties arose, he transferred his interest to the Cambridge Scientific Instrument Company in London, England. The machines manufactured by this famous company began to reach laboratories in 1908.[1]

This transfer of business arrangements made access to the machines easier and led to the early appearance of the electrocardiograph in Canada through Dr. Julian Loudon, who orchestrated the introduction of the first electrocardiograph machine to this country.

Julian Derwent Loudon, physician-in-chief of St. Michael's Hospital, Toronto, 1921–1945. (Courtesy of St. Michael's Hospital Archives)

Julian Derwent Loudon was born in Toronto on May 27, 1881. His father, James Loudon, was professor of physics at the University of Toronto and later became that university's first Canadian-born president. Loudon senior's first discipline was mathematics, but he later moved into physics (particularly, geometric optics). He became the president of the Canadian Institute, an organization whose purpose was to popularize science by presenting demonstrations and lectures. He later became president of the American Association for the Advancement of Science.[2]

James Loudon, father of Julian Loudon, and the first Canadian-born president of the University of Toronto. (Courtesy of the University of Toronto Archives)

After Julian Loudon received his MB in 1906, he went abroad – to London, England – for postgraduate work. This was both unusual and expensive and required financial resources that were likely provided by his family. During the next 5 years, he worked in several hospitals, including the London Hospital (Whitechapel) and the Victoria Hospital for Diseases of the Chest.[3]

Luckily, his time there coincided with the early growth of electrocardiography in England. Thomas Lewis, the famous British clinical scientist, obtained a string electrocardiograph in 1908. With the help of a young American physician, Alfred Cohn, he set it up in the basement of London's University College Hospital and began his early experiments.[4] Loudon must have been exposed either directly or indirectly to the work of the brilliant but eccentric Welshman. They were the same age, and while Loudon worked as the resident physician at the London Hospital, Lewis started his consulting career as an outpatient physician there.

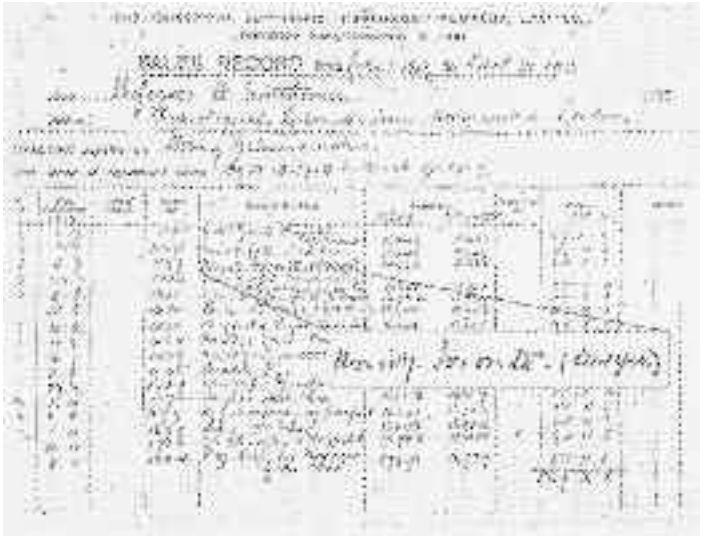
Lewis's mentor, James Mackenzie, had an appointment at the Victoria Hospital when he moved to London in 1908. Loudon spent a year there. Mackenzie's "critical attitude to medicine and his independence of authority" were like oxygen to Lewis.[5] He was influential in stimulating Lewis in his scientific career path. Whatever contacts Loudon had with these men, the atmosphere was enough to stimulate his interest in electrocardiography.

In 1912, Loudon returned to St. Michael's Hospital in Toronto to practise as a consultant in medicine. The hospital was small and was still in the shadow of Toronto General Hospital. Within a year, Loudon had convinced the Sisters of St. Joseph and the hospital board that they should purchase an electrocardiograph. However, the instrument was unavailable in Canada.

It is generally conceded that the first electrocardiograph was set up at Montreal General Hospital by Thomas Cotton.[4,6] Cotton, a McGill University graduate, had worked directly with Lewis. At about the same time, he urged the purchase of an electrocardiograph at Montreal General Hospital but ran into a stone wall. Only after Sir William Osler had written a letter of support (and even offered to contribute) was Cotton able to secure the purchase. The instrument was installed in 1914.[4,6] However, the Loudon electrocardiograph had been dispatched from England in July 1913. A copy of the original sales order from the Cambridge Scientific Instrument Company at the former Academy of Medicine Museum in Toronto indicates St. Michael's Hospital as the first purchasing institution in Canada. Dr. R. J. Dwyer, the first physician-in-chief at St. Michael's, received the machine, sent on July 11. Machines were sent to Toronto General Hospital on September 15 and to Montreal General Hospital on December 12 of that same year.

By July 1914, Loudon had published an article in the *Canadian Practitioner and Review* on clinical electrocardiography (along with illustrations of electrocardiograms produced at St. Michael's Hospital).[7] The article itself was described by Segall as containing "the material of a textbook in miniature."[4]

Given the quality of his training – and his pedigree as the son of a former university president – it is surprising that Loudon assumed a position at St. Michael's rather than at the more prestigious Toronto General.



Sales record of the Cambridge Scientific Instrument Company, showing the date of dispatch of the St. Michael's electrocardiograph to R. J. Dwyer, the hospital's head physician at the time. (Courtesy of St. Michael's Hospital Archives)

However, Loudon's father (who retired in 1906) had been an unpopular president; he had irritated Joseph Flavelle, the chairman of the board at Toronto General, by supporting some prominent clinicians who had been left out of a reorganization in 1913.[8]

Loudon's early grasp of the use of the electrocardiograph in diagnosis is shown in a case reported in 1915 in the *Canadian Medical Association Journal*. A teenaged Macedonian sausage maker had enlarged lymph nodes and a leukocytosis, and radiographic examination showed transposition of the viscera. Loudon confirmed the transposition of the heart with the electrocardiograph.[9]

In the 1914–15 report of the hospital's electrical department to the hospital's Medical Advisory Committee, Loudon described the installation of the machine "two years ago." The same report propounds Loudon's view that the electrocardiograph was now an essential part of hospital care.[10] When his 1914 review of electrocardiography was published, there may have been four machines in the whole country. Whom did he see as his readers? This again suggests that he was seeking to convince clinicians of the necessity of the electrocardiograph in hospital clinical care.

A scholarly man, Loudon helped establish a hospital journal and contributed to it. He cowrote a book describing a system for case taking that was published by Macmillan, and a monograph on a systematic scheme for the examination of the neurologic system was published in 1912 (at least two copies still exist).[10–12]

Following the Great War, the appointment of the autocratic Duncan Graham to the Sir John and Lady Eaton Chair of Medicine at Toronto General Hospital led to a purging of very prominent University of Toronto medical staff. Loudon survived the purge, probably because he embodied Graham's view of the modern university clinician. He brought science into patient care and was systematic in gathering histories and conducting examinations.[13]

Loudon remained a generalist, and his interest in cardiology may have waned; many of his subsequent publications concerned neurology.[9] While his private practice was never large, he was greatly respected by both students and fellow clinicians for his medical knowledge. In 1921, he was appointed physician-in-chief at St. Michael's Hospital. He also served as a consultant to the hospital nursing school and acted as a coroner for the City of Toronto. His tenure as department head ended in 1945. He succumbed to carcinoma of the cecum and died in Toronto in October 1959.[10]

Although he is viewed as a pioneer in Canadian cardiology, Loudon was in reality a generalist. In recognizing the role of the electrocardiograph in bringing physiology to the bedside, and in his systematic assembling of history and physical examination, he exemplified the new scientifically trained clinician of the early 20th century.

Acknowledgements

The author would like to thank Marina Englesakis, former archivist at St. Michael's Hospital, for her help and Francine Garraway and Maureen Fuentes for manuscript transcription.

References

1. Rautaharju PM. A hundred years of progress in electrocardiography. 1: Early contributions from Waller to Wilson. Can J Cardiol 1987;3:362–74.
2. University of Toronto Archives, James Loudon. B72-0031/011.
3. Middleton JE. The Municipality of Toronto: A History, Volume 2. Toronto (ON): Dominion Publishing Company, 1923.
4. Segall HN. Introduction of electrocardiography in Canada. Can J Cardiol 1987;3:358–61.
5. Drury AN, Grant RT, eds. Obituary, Thomas Lewis 1881–1945. Obituary notices of Fellows of the Royal Society. www.jstor.org. Accessed November 3, 2010.
6. Roland CG. Profiles in cardiology. Thomas Forrest Cotton (1884–1965). Clin Cardiol 2007;30:366–8.
7. Loudon J. Clinical electrocardiography. Can Practitioner Rev 1914;3:407–17.
8. Friedland ML. The University of Toronto: A History. Toronto (ON): University of Toronto Press; 2003.
9. Proceedings of the Section of Medicine. Academy of Medicine, Toronto. CMAJ 1915;5:73–4.
10. St. Michael's Hospital Archives. Julian Loudon. H-3, 12.
11. Loudon JD. Examination of the Nervous System. Toronto (ON): G. A. Merrick Printing; 1912.
12. Ross GW, Loudon JD. A System for Case Taking with Explanatory Notes. Toronto (ON): Macmillan; 1916.
13. Kerr RB, Waugh D. Duncan Graham: Medical Educator and Reformer. Toronto (ON): The Hannah Institute and Dundurn Press; 1989.

Atypical Femur Fracture in a Liver Transplant Recipient on Long-Term Bisphosphonate Therapy

Daniel Banaszek BSc, Suzanne Morin MD

About the Authors
Daniel Banaszek is a medical student, and Suzanne Morin is an internist, both at McGill University, in Montreal, Quebec. Correspondence may be directed to suzanne.morin@mcgill.ca.

Case Report

A 68-year-old Chinese male, the recipient of a liver transplant in 1994, presented to the emergency department following a non-traumatic fracture of the left proximal femur. While chatting with friends, he had attempted to sit on the hood of his car. He felt intense pain in his upper thigh and subsequently could not bear weight on the injured leg (Figure 1). He denied trauma to the leg at the time or in the days preceding the event. He denied any previous fractures.

The patient had undergone an uncomplicated liver transplantation in 1994 for hepatitis B–associated hepatocellular carcinoma, and received long-term immunosuppressive therapy. He used prednisone for a few years, following the transplantation. He had been taking alendronate, calcium, and vitamin D for prevention of corticosteroid-induced osteoporosis since 1996. His other medications included lamivudine, pantoprazole, ramipril, atorvastatin, and ezetimibe. In the weeks prior to the fracture, the patient admitted to persistent left thigh pain upon weight bearing, particularly upon climbing stairs.

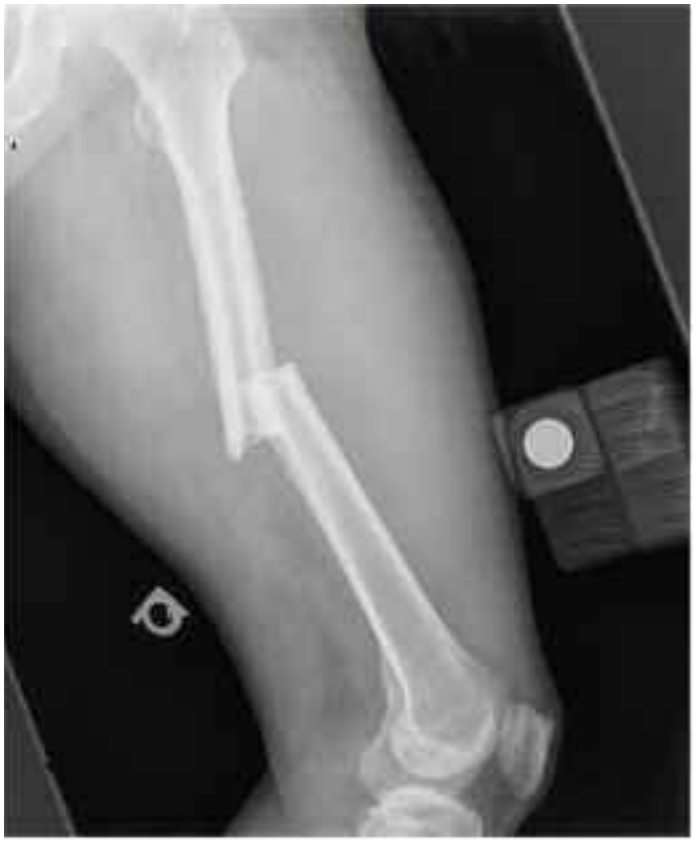


Figure 1. Diaphyseal non-comminuted femur fracture, abnormally thickened cortices are also noted.

In the emergency room, a radiograph of his left leg revealed a transverse, non-comminuted, mid-diaphyseal fracture of the femur. The cortices of the femur were also reported to be abnormally thickened. The right femur was normal. The patient underwent surgical repair of his fracture; his post-operative course was uneventful, and he was discharged to a rehabilitation hospital within 4 days. He had undergone a bone mineral density (BMD) measurement 2 years previously, which was reported as T-scores of −1.4 at the femoral neck and of −1.0 at the lumbar spine. Serum 25-hydroxy-vitamin D, parathyroid hormone, calcium, phosphate, renal function, serum protein electrophoresis, and TSH done during his hospital stay were all within normal limits. Investigations were negative for bone metastasis and other less prevalent metabolic anomalies (such as hypophosphatasia). A diagnosis of atypical femur fracture was made, and bisphosphonate therapy was discontinued.

Atypical Femur Fractures

Hip fracture is the most serious consequence of osteoporosis; it requires hospitalization and causes significant disability, morbidity, and excess mortality.[1] Its incidence increases with age in both men and women, and it is linked with a low BMD and an increased likelihood of falling. Approximately 30,000 hip fractures occur in Canada each year, and more than 90% of these fractures are attributed to osteoporosis. The annual costs associated with hip fractures in Canada were estimated to be $650 million in 2001 and continue to increase.[2,3] Most studies have considered fractures of the proximal aspects (femoral neck, intertrochanteric and subtrochanteric regions) of the femur collectively. However, some have reported that there are variations in the pathophysiology, risk factors, treatment, and prognosis associated with different subtypes of femoral fractures. Those fractures that occur within the capsule are termed intracapsular femoral neck fractures (up to 54% of total fractures); fractures outside the joint are divided into intertrochanteric (up to 50%) and those that occur further down the femur at the junction with the femoral shaft, subtrochanteric and diaphyseal (6–30%). Subtrochanteric (defined as a femur fracture within 5 cm distal to the lesser trochanter) and diaphyseal fractures are commonly thought to be the result of high-energy trauma because of the biomechanical resiliency of these regions.[4] However, their incidence has recently been documented to rise

Table 1. Atypical Femoral Fracture: Major and Minor Features

Major Features*
• Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
• Associated with no trauma or minimal trauma, as in a fall from a standing height or less
• Transverse or short oblique configuration
• Non-comminuted
• Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
Minor Features†
• Localized periosteal reaction of the lateral cortex, known as "beaking"
• Generalized increase in cortical thickness of the diaphysis
• Prodromal symptoms, such as dull or aching pain in the groin or thigh
• Bilateral fractures and symptoms
• Delayed healing
• Comorbid conditions: vitamin D deficiency, rheumatoid arthritis, hypophosphatasia
• Use of pharmaceutical agents: bisphosphonates, proton pump inhibitors, glucocorticoids
• Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumours, and periprosthetic fractures

*Must all be present for diagnosis of an atypical fracture.

†Not required but often observed in atypical fractures.

exponentially with age, and they have been increasingly documented in patients with osteoporosis. Knowledge of the clinical variables associated with subtrochanteric and diaphyseal fractures, in contrast with the more common proximal femoral neck and intertrochanteric fractures, is lacking. Studies are ongoing to expand the science in this area.

Bisphosphonates (alendronate, risedronate, and zoledronic acid) are recommended as front-line agents to reduce fracture risk in patients with osteoporosis and have had, in general, an excellent safety profile.[5] However, recent reports have noted that prolonged use of bisphosphonates may be associated with rare but serious adverse effects, namely *atypical femur fractures* (AFFs), an atraumatic subset of subtrochanteric and diaphyseal femur fractures. The American Society of Bone and Mineral Research (ASBMR) task force has defined AFF as atraumatic transverse or oblique fractures extending across the entire femoral shaft, often with the formation of a medial spike and, in certain cases, a radiographic pattern of cortical thickening of the diaphysis. In some cases, the fracture is incomplete and involves only the lateral cortex (Table 1).[6] In addition to bisphosphonates, co-morbid conditions such as vitamin D deficiency, hypophosphatasia, and diabetes and the use of glucocorticoids and proton pump inhibitors have been associated with AFF. To be defined as an AFF, all major criteria should be present; minor criteria are often observed but not required for diagnosis. Although AFFs are most commonly brought to medical attention in the setting of bisphosphonate use, no definite causal relationship has thus far been established.

Unlike most medications, bisphosphonates remain in the body for decades. After ingestion, these compounds are either excreted through the kidneys or are deposited on metabolically active surfaces of bone. There, they strongly inhibit osteoclastic bone resorption by interfering with a cell's cytoskeleton and causing apoptosis. Because bone resorption is tightly coupled to bone formation during the bone remodelling cycle, bisphosphonates also limit bone formation. This leads to increased BMD (through lower bone turnover and enhanced mineralization of the bone matrix), lower trabecular plate perforation rate, and overall improved bone strength, as demonstrated by reduced fracture risk. Ten-year results from extension studies of the first large pivotal alendronate efficacy trials have demonstrated sustained beneficial effects on bone density and fracture reduction, without serious adverse events.[7] Although the optimal duration of treatment is not established, clinicians do not usually consider discontinuing therapy in patients who have sustained a fracture or who have very low bone density; consequently, adherent patients may remain on therapy for extended periods of time. Perhaps when exposed to bisphosphonates for a prolonged period, the bone becomes over-mineralized and demonstrates a reduced ability to self-repair.

The most problematic issue with conducting studies into AFFs is their very rare occurrence. The ASBMR task force has documented that only 7–10% of all hip fractures occur in the subtrochanteric or femoral shaft region and, of these, only 17–29% can be classified as atypical. Moreover, as atypical fractures are most often reported in the setting of bisphosphonate use, there may be underreporting of their incidence outside this setting.

The US Food and Drug Administration recently convened a meeting of scientists, clinicians, and patient groups to review and discuss the available data regarding the long-term (greater than 3–5 years) use of bisphosphonates for the treatment and/or prevention of osteoporosis in light of adverse events potentially related to their use (not only AFF but also osteonecrosis of the jaw and esophageal cancer). The final recommendations are not yet available, but it is anticipated that clinicians will be encouraged to review the necessity to pursue therapy after approximately 5 years of continuous bisphosphonate use. Currently, Osteoporosis Canada recommends that only patients at high risk (as determined by a 10-year absolute risk for fracture of ≥20%) and selected patients at moderate risk (10–20%) be offered pharmacological therapy to reduce their risk for fractures.[5] In these patients, it has been shown that the benefits far outweigh the risk of rare adverse events. Because of the absence of scientific data regarding optimal duration of therapy with bisphosphonates, Osteoporosis Canada recommends against treatment interruptions (drug holiday) in patients who have had previous fragility fractures (especially of the hip and the vertebrae), whose bone mineral density is very low, or who have risk factors that put them in the higher-risk category.

Conclusion

Osteoporosis-related fractures are frequent and a cause of disability, pain, and substantial personal and economic costs. Bisphosphonates can reduce the risk of fractures in patients who have a 10-year absolute high and moderate risk for fractures and have, in general, a favourable safety profile when used for up to 3–5 years. Longer-term use carries the risk of very rare, but serious adverse events and should probably be re-evaluated

annually. Clinicians should be alerted when patients on long-term bisphosphonate therapy complain of groin or thigh pain and proceed with imaging (radiographs of both femurs and bone scintigraphy). Bisphosphonates should be discontinued in patients in whom an atypical fracture is documented. A call for patient registries and international collaboration has been issued from many organizations, and we and other Canadian researchers are actively participating in this endeavour.

References

1. Morin S, Lix LM, Azimaee M, et al. Mortality rates after incident non-traumatic fractures in older men and women. Osteoporos Int 2011;22:2439–48.
2. Wiktorowicz ME, Goeree R, Papaioannou A, Adachi JD, Papadimitropoulos E. Economic implications of hip fracture: health service use, institutional care and cost in Canada. Osteoporos Int 2001;12:271–8.
3. Leslie WD, Metge CJ, Azimaee M, et al. Direct costs of fractures in Canada and trends 1996–2006: a population-based cost-of-illness analysis. J Bone Miner Res 2011;26(10):2419–29.
4. Nieves JW, Bilezikian JP, Lane JM, et al. Fragility fractures of the hip and femur: incidence and patient characteristics. Osteoporos Int 2010;21:399–408.
5. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010;182:1864–73.
6. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2010;25:2267–94.
7. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350:1189–99.

2011 Canadian Hypertension Education Program Update

- ***All Canadian adults need to have blood pressure (BP) assessed at all appropriate clinical visits.*** More than one in five adult Canadians has hypertension and the lifetime risk of developing hypertension is approximately 90%. All adults require ongoing assessment of blood pressure throughout their lives. People with hypertension need to be encouraged and taught how to monitor their blood pressure at home. People with high normal blood pressure require annual assessment.
- ***Lifestyle modifications are effective in preventing hypertension, treating hypertension, and reducing cardiovascular risk.*** Blood pressure is lowered and other cardiovascular risks can be favourably impacted by a healthy diet, regular physical activity, moderation in alcohol consumption, reductions in dietary sodium, and in some, stress reduction. Hypertensive patients should live and work in a healthy tobacco-free environment. Brief health care professional interventions that are individualized to the circumstances of the person with hypertension increase the probability of lifestyle change.
- ***Optimum management of BP requires assessment of overall cardiovascular risk.*** Over 90% of Canadians with hypertension have other cardiovascular risks. Identifying and successfully managing these other risks including high dietary sodium, smoking, unhealthy diet, physical inactivity, abdominal obesity, dyslipidemia, and dysglycemia can reduce cardiovascular events by over 60% in hypertensive patients. Indicating the risk relative to similar sex-aged Canadians as a vascular age can improve patients' understanding and risk management.
- ***Treat to target.*** Blood pressure should be consistently lower than 140/90 mmHg in most patients and consistently lower than 130/80 mmHg in those with diabetes or chronic kidney disease.
- ***Combinations of both lifestyle change and drugs are generally necessary to achieve target blood pressures.*** Most people with hypertension require lifestyle change and antihypertensive drug combinations to achieve recommended blood pressure targets. Diuretics are nearly always required to treat hypertension especially when "resistant." Many people with diabetes or chronic kidney disease require three or more antihypertensive drugs including diuretics to achieve blood pressure targets. Regular follow-up and titration of therapy are required to achieve blood pressure targets.
- ***Focus on adherence.*** Non-adherence to lifestyle and pharmacotherapy is an important cause of poor blood pressure control. Patient adherence to lifestyle and pharmacotherapy should be assessed on each visit and interventions to improve adherence should be a part of clinical routine.
- ***Promote healthy public policies to prevent hypertension.*** Health care professionals and their organizations need to more actively work with different levels of government to implement healthy public policies and health services policies, and build community capacity to promote healthy behaviour and prevent high blood pressure.
- ***Sign up at www.htnupdate.ca to access the latest hypertension resources.*** Sign up to be notified by e-mail when hypertension resources are updated or developed at www.htnupdate.ca or download the current resources from www.hypertension.ca/tools. Become a Hypertension Champion and deliver CHEP web-based CME programs at your regular educations rounds. www.htnupdate.ca will give you an opportunity to interact with top Canadian hypertension experts.
- ***Have your patients sign up at www.myBPsite.ca to access the latest hypertension resources.*** Canadians who register become members of a new website specifically designed for patients with hypertension. MyBP will allow your patients to automatically receive new educational resources.

Detailed information on the 2011 Canadian Hypertension Education Program Recommendations for you and your patients can be obtained by signing up at www.htnupdate.ca.

Internal Medicine: Life in the Fast Lane

William Connors MD

About the Author
William Connors is a 2nd-year internal medicine resident in the University of Calgary, in Calgary, Alberta. Correspondence may be directed to wjaconnors@gmail.com.

"Life moves pretty fast. If you don't stop and look around once in a while, you could miss it." These were surprisingly wise words from an '80s pop film.[1] As I lay exhausted and content on a remote beach off the West Coast of British Columbia, I realized just how true this quotation is. A sunset with the soundtrack of crashing waves was the perfect setting to reflect upon a year I could hardly believe had already passed. Within weeks, I would be a senior resident in the University of Calgary's Internal Medicine Program. How could this have snuck up on me? How did I get here?

Gazing out at the endless blue ocean as it curled beyond the horizon, I was pleasantly far away from the beeping of pagers and bustle of the hospital. I was 3 days and 35 mud-filled kilometres into a long-awaited hike down the west coast of Nootka Island, British Columbia. An island off an island – Vancouver Island – Nootka is blissfully isolated, with a roughly cut coastal trail winding down its western face. The Nootka trail is one of a series of coastal hikes along the province's rugged coastline that I had long wanted to explore. And the timing couldn't have been better.

Together with a mixed group of kayakers and hikers, I spent a week exploring this stretch of heaven. It rained, the mud was deep, my feet blistered up, and I loved every bit of it. The exercise and simplicity of backpacking provided the perfect frame of mind to take stock of my journey thus far. It had been quite a year. I had made the move to the eastern slope of the Rockies and finally become comfortable – or at least more so – referring to myself as doctor. Alongside an exceptional group of colleagues, I had become part of a vibrant and inclusive medical community in Calgary. But beyond the new title and environment, there was something more personal that had defined my experience.

Looking back over the year, it was faces that stood out most. The frail Russian woman with fiery eyes and a warming smile who had awoken from a hyperglycemic hyperosmolar coma; the grandfatherly veteran with a firm handshake who had fought through life-threatening urosepsis; the innocent college student with lists of questions who had clung to life during an episode of thrombotic thrombocytopenic purpura. These were the patients, among many others, who had defined and driven my first year of residency. And it all went by so fast.

I returned from this hike reinvigorated and excited, not only from the experience but also from what I then realized had actually happened over the past year. Sometimes we need to stop and look around to appreciate how we arrived where we are.

I am now that senior resident, as nervous and vigilant as ever, but slowly gaining confidence with the help of exceptional patients and teachers. I will certainly do more hikes and take the time to look around, as I plan not to miss any part of this special journey.

Reference

1. Ferris Bueller's Day Off (Paramount Pictures): videoclip available at www.youtube.com/watch?v=HbR7axof1wk. Accessed December 9, 2011.

BRILINTA®
ticagrelor tablets

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Platelet Aggregation Inhibitor

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

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

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

CONTRAINDICATIONS: BRILINTA (ticagrelor) is contraindicated in:

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

SPECIAL POPULATIONS:

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

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

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

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

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

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

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

Safety Information

WARNINGS AND PRECAUTIONS:

General

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

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

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

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

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

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

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

Peri-Operative Considerations

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

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

Respiratory

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

ADVERSE REACTION SERIOUSNESS AND INCIDENCE:

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

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

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

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

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

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

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

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

Administration

Recommended Dose and Dosage Adjustment

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

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

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

Missed Dose

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

SUPPLEMENTAL PRODUCT INFORMATION

WARNINGS AND PRECAUTIONS:

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

Cardiovascular

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

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

Neurologic

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

Peri-Operative Considerations

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

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

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

Adverse Drug Reaction Overview

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

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

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

Clinical Trial Adverse Drug Reactions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS:

Drug-Drug Interactions

Effects of Other Drugs on BRILINTA

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

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

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

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

Effects of BRILINTA on Other Drugs

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

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

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

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

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

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

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

DOSAGE AND ADMINISTRATION:

General

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

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

Recommended Dose and Dosage Adjustment

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

Dosing Considerations in Special Populations

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

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

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

OVERDOSAGE:

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

Treatment

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

ACTION AND CLINICAL PHARMACOLOGY:

Pharmacodynamics

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

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

Pharmacokinetics

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

Date of Preparation: May 26, 2011

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

AstraZeneca Canada Inc.
1004 Middlegate Road
Mississauga, Ontario L4Y 1M4
www.astrazeneca.ca

Levemir®

(insulin detemir)

House Standard Solution for Injection 100 U/mL

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Antidiabetic Agent

INDICATIONS AND CLINICAL USE

Levemir® (insulin detemir) is indicated for:

- the treatment of adult patients with type 1 or type 2 diabetes mellitus who require a long-acting (basal) insulin for the control of hyperglycemia;
- the treatment of pediatric patients with type 1 diabetes mellitus who require a long-acting (basal) insulin for the control of hyperglycemia. The safety and efficacy of **Levemir**® has not been studied in children below the age of 6 years.
- the treatment of type 2 diabetes mellitus in combination with oral anti-diabetic agents (OADs) [metformin or sulfonylureas] in adult patients who are not in adequate metabolic control on OADs alone. For safety reasons, the use of insulin in combination with thiazolidinedione is not indicated (See Supplemental Product Information, DRUG INTERACTIONS).

Recommended in combination with short - or rapid-acting meal time insulin.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

Levemir® (insulin detemir) is contraindicated during episodes of hypoglycemia (see **Supplemental Product Information** - HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE).

Safety Information

WARNINGS AND PRECAUTIONS

General

Hypoglycemia is the most common adverse effect of insulin, including **Levemir**®.

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Usually the first symptoms of hyperglycemia develop gradually over a period of hours or days. They include thirst; increased frequency of urination; nausea; vomiting; drowsiness; flushed dry skin; dry mouth; loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycemic events eventually lead to diabetic ketoacidosis, which is potentially lethal. Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement. Transferring a patient to another type or brand of insulin should be done under medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human, human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage. Patients taking **Levemir**® (insulin detemir) may require a change in dosage from that used with their usual insulin. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Levemir® should not be administered intravenously as it may result in severe hypoglycemia. **Levemir**® is not to be used in insulin infusion pumps. Absorption after intramuscular administration is faster and greater than absorption after subcutaneous administration. Insulin may cause sodium retention and edema particularly if previously poor metabolic control is improved by intensified insulin therapy. When using **Levemir**® in combination with oral anti-diabetic agents (OADs)) metformin or sulfonylureas, please refer to the respective product monograph for OADs for their Warnings and Precautions Information.

Mixture with other Insulin

Levemir® **should not be mixed with other insulin for injection.** If **Levemir**® is mixed with other insulin preparations the profile of action of one or both individual components will change. Mixing **Levemir**® with a rapid-acting insulin analogue like NovoRapid® (insulin aspart), results in an action profile with a lower and delayed maximum effect compared to separate injections.

Special Populations and Conditions

Hepatic Insufficiency: Individuals with severe hepatic dysfunction, without diabetes, were observed to have lower AUCs as compared to healthy volunteers. Caution should be taken when making general dosing recommendations for subjects with liver impairment. As with other insulin preparations, titration with **Levemir**® and glucose monitoring should be intensified in patients with liver impairment.

Renal Insufficiency: There was no clinically relevant difference in pharmacokinetics of **Levemir**® between subjects with renal impairment and healthy subjects.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Adverse drug reactions observed in patients using **Levemir**® are mainly dose-dependent and are due to the pharmacologic effect of insulin. Hypoglycemia is a common undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. From clinical investigations it is known that major hypoglycemia, defined as requirement for third party intervention, occurs in approximately 6% of adult patients treated with **Levemir**®. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. Injection site reactions are seen more frequently during treatment with **Levemir**®, than with human insulin. These reactions include redness, inflammation, bruising, swelling and itching at the injection site. Most of the injection site reactions are minor and of a transitory nature, i.e. they normally disappear during continued treatment in a few days to a few weeks.

Adverse Drug Reactions in Adult and Paediatric Patients

The overall percentage of adult patients treated with **Levemir**® expected to experience adverse drug reactions is estimated to be 12%. In the clinical study in pediatric subjects aged 6 to 17 years; adverse drug reactions were reported for 9.5% of patients treated with **Levemir**®.

Drug Interactions

As with insulins in general, concomitant use of other drugs may influence insulin requirements. (**See Supplemental Product Information**)

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

Administration

DOSAGE

Dosing Considerations

Levemir® should be used once-daily in combination with oral antidiabetic drugs (OADs); or short- or rapid-acting meal time insulin. When **Levemir**® is used as part of a basal-bolus insulin regimen, **Levemir**® has the option of being administered twice daily, depending on patients' needs. For patients who require twice daily dosing to optimise blood glucose control, the evening dose can be administered either with the evening meal or at bedtime. Dosage of **Levemir**® is individual and determined, based on the physician's advice, in accordance with the needs of the patient.

Recommended Dose and Dosage Adjustment

New Patients: Patients being initiated on insulin for the first time can be started on **Levemir**® in the same manner as they would be on human insulin.

Type 2 patients adding Levemir® to OAD:

In combination with oral antidiabetic agents, it is recommended to initiate **Levemir**® treatment with once-daily administration at a dose of 10U or 0.1-0.2U/kg. The dose of **Levemir**® should be titrated on individual patients' needs.

Transfer Patients: When patients are transferred from other insulin to **Levemir**®, the change should be made as directed by the physician. Patients transferring to **Levemir**® from intermediate or long-acting insulin may require adjustment of dose and timing of administration to achieve glycemic target. Close glucose monitoring is recommended during the transition and in the initial weeks thereafter. Concomitant anti-diabetic treatment may need to be adjusted (dose and timing of concurrent short-acting insulins or the dose of oral anti-diabetic agents, see **Safety Information** - WARNINGS AND PRECAUTIONS, General)

Study References

1. Levemir® Product Monograph, Novo Nordisk Canada Inc., 2009. **2.** Philis-Tsimikas A, Charpentier G, Clauson P *et al.* Comparison of Once-daily Insulin Detemir with NPH Insulin Added to a Regimen of Oral Antidiabetic Drugs in Poorly Controlled Type 2 Diabetes. *Clinical Therapeutics* 2006;28(10):1569-1581. † 20-week, randomized, open-label, parallel trial comparing Levemir® to NPH as add-on therapy to OADs in insulin-naïve patients with type 2 diabetes; n=504. **3.** Montañana CF, Herrero CH, Fernández MR *et al.* Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight Type 2 diabetes patients – The PREDICTIVE™ BMI clinical trial. *Diabetic Medicine* 2008;25:916-923. ‡ 26-week, treat-to-target trial in 277 type 2 patients randomized to receive either Levemir® or NPH at bedtime and NovoRapid® at mealtimes.

Supplemental Product Information

WARNINGS AND PRECAUTIONS

Hypoglycemia

As with other insulins, hypoglycemia is the most common adverse effect of insulin therapy, including **Levemir**®.

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

Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see **Safety Information** - ADVERSE REACTIONS and **Supplemental Product Information** - HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE). Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia. Glucose monitoring is recommended for all patients with diabetes.

Carcinogenesis and Mutagenesis

See **Product Monograph**, Part II: SCIENTIFIC INFORMATION – TOXICOLOGY.

Hepatic/Biliary/Pancreas

Hepatic Impairment: As with other insulins, the requirements for **Levemir**® may need to be adjusted in patients with hepatic impairment (see Safety Information – WARNINGS AND PRECAUTIONS – Special Populations and Conditions)

Immune

Local Allergic Reaction: As with any insulin therapy, injection site reactions may occur and include pain; itching; hives; swelling and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of **Levemir**®.

Systemic Allergic Reaction: Systemic allergic reactions have rarely occurred with insulin treatment. These reactions may be characterized by a generalized rash (with pruritus); shortness of breath; wheezing and a drop in blood pressure. Severe cases of generalized allergy including anaphylactic reaction may be life threatening. Insulin administration may cause formation of insulin antibodies. A positive correlation was observed in clinical trials between the dose of **Levemir**® (insulin detemir) and the formation of insulin detemir specific antibodies, but this did not appear to affect HbA1c. The long term impact of insulin detemir antibodies on glycemic control is under investigation (see **Product Monograph** PART II: CLINICAL TRIALS).

Renal

Renal Impairment: As with other insulins, the requirements for **Levemir**® may need to be adjusted in patients with renal impairment (see **Safety Information** – WARNINGS AND PRECAUTIONS – **Special Populations and Conditions**)

Special Populations

Pregnant Women: There is no clinical experience with **Levemir**® during pregnancy or lactation. Animal reproduction studies have not revealed any differences between **Levemir**® and human insulin regarding embryotoxicity and teratogenicity. In general, intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy

and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimester. After delivery, insulin requirements normally return rapidly to pre-pregnancy values.

Nursing Women: It is unknown whether **Levemir**® is excreted in significant amounts in human milk. For this reason, caution should be exercised when **Levemir**® is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan or both.

Geriatrics: There was no clinically relevant difference in pharmacokinetics of **Levemir**® between elderly and young subjects. As with all insulins, in elderly patients and patients with renal or hepatic impairment, glucose monitoring should be intensified and insulin detemir dosage adjusted on an individual basis.

Pediatrics: The pharmacokinetic properties of **Levemir**® were investigated in children (6-12 years) and adolescents (13-17 years) and compared to adults with type 1 diabetes. The pharmacokinetic properties were similar in the three groups. The efficacy and safety of **Levemir**® were demonstrated in children and adolescents aged 6 to 17 years. No evaluated pediatric efficacy and safety data are available to support pediatric dosing advice below the age of 6 years.

Monitoring and Laboratory Tests

As with all insulin therapy, the therapeutic response to **Levemir**® should be monitored by periodic blood glucose tests. Glycosylated hemoglobin should be measured every 3 to 4 months in all patients taking insulin.

Information for Patients

Patients should be informed about the potential advantages and disadvantages of **Levemir**® (insulin detemir) therapy including possible side effects. Patients should also be offered continued education and advice on insulin therapies, delivery device options, life-style management, self-monitoring, complications of insulin therapy, timing of dosage, instruction for use of injection devices and storage of insulin. To obtain optimal glycemic control, the need for regular blood glucose self-monitoring should be considered when using **Levemir**®.

Female patients should be advised to discuss with their physician if they are pregnant or if they intend to become pregnant.

ADVERSE REACTIONS

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

Levemir® has been evaluated for safety in 3747 subjects treated for type 1 or type 2 diabetes: 518 in pharmacology trials, 195 in short-term trials and 3034 in the intermediate and long-term trials (including Trials 1385, 1372 and 1379). An additional 862 subjects were exposed to **Levemir**® during three (intermediate and long-term) phase 3 trials in which **Levemir**® was used as an add-on treatment to oral antidiabetic drugs (OADs) in subjects with type 2 diabetes (data summarized below). In controlled clinical trials, discontinuation due to adverse events occurred in 1.7% of subjects with **Levemir**® and in 1.1% of subjects treated with comparators (mainly NPH insulin). In controlled clinical trials, adverse drug reactions reported in children and adolescents with type 1 diabetes aged 6-17 years were similar to those observed in adult patients. The overall frequency, however, of major hypoglycemic episodes requiring third party assistance was higher in this age group (16% with **Levemir**®, and 20% with NPH insulin). Only few of these episodes were reported as adverse drug reactions. Serious adverse events reported with **Levemir**®, and NPH insulin in pediatric subjects (irrespective of correlation to trial products) included: gastroenteritis (2.2 vs. 0%), bone fractures (0.9 vs. 0%), ketosis (1.3 vs. 1.9%), accidental injury (0.4 vs. 1.7%) and convulsions (0.9% in both groups).

Serious Adverse Events with Possible or Probable Relationship to Trial Drug No serious adverse events with possible or probable relation to trial drug were reported with **Levemir**® or NPH insulin in ≥1% of subjects.

The following serious adverse events with possible or probable relationship to trial drug were reported at an incidence of < 1% for **Levemir**® and NPH insulin in controlled clinical trials (in more than 1 subject, with higher frequency with **Levemir**® than with NPH insulin):

Metabolic and nutritional disorders: hyperglycemia.

Adverse Events Regardless of Relationship to Trial Drug

Table 1 – Adverse events reported with **Levemir**® and NPH insulin occurring in ≥1% of subjects regardless of drug relationship.

System Organ Class	Levemir® n=3747 (%)	NPH insulin n=2084 (%)
Respiratory System Disorders		
Upper Respiratory Tract Infection	16.4	16.3
Pharyngitis	5.2	5.3
Bronchitis	2.4	2.1
Rhinitis	2.2	2.4
Sinusitis	2.0	2.1
Coughing	2.0	1.8
Central and Peripheral Nervous System Disorders		
Headache	16.0	14.5
Dizziness	1.8	0.9
Gastro-intestinal System disorders		
Abdominal pain	4.2	3.0
Diarrhoea	3.2	4.2
Nausea	3.0	2.6
Gastroenteritis	3.4	3.1
Vomiting	1.9	2.1
Toothache	1.5	1.6
Dyspepsia	1.2	1.8
Body as a Whole - General Disorders		
Influenza-like Symptoms	5.4	5.4
Back Pain	3.3	3.0
Fatigue	1.5	0.9
Fever	1.4	1.2
Pain	1.2	0.9
Musculo-Skeletal System Disorders		
Arthralgia	1.9	1.9
Skeletal Pain	1.0	1.3
Myalgia	0.7	1.4
Resistance Mechanism Disorders		
Viral Infection	2.0	2.2
Infection	1.2	1.4
Vision Disorders		
Retinal Disorder	2.4	2.4
Conjunctivitis	0.7	1.1
Secondary Terms		
Accidental Injury	3.0	3.2
Other Events	1.1	0.0
Metabolic and Nutritional Disorders		
Hypoglycemia	1.4	0.8
Application Site Disorders		
Injection site reaction	1.7	0.6
Urinary System Disorders		
Urinary tract infection	1.5	1.3
Cardiovascular Disorders, General		
Hypertension	0.8	1.0
Reproductive Disorders, Female		
Dysmenorrhoea	1.1	0.9

Adverse Events in Trials of Levemir® in Combination with Oral Antidiabetic Drugs (OADs) Three intermediate and long-term phase 3 trials (NN304-1632, NN304-1373, NN304-1530) were conducted, in which **Levemir**® was used as an add-on treatment to oral antidiabetic drugs (OADs) in subjects with type 2 diabetes. A total of 862 subjects with type 2 diabetes were exposed to **Levemir**® during these three studies. The percentage of subjects reporting adverse events with insulin detemir was 56%, NPH insulin was 49% and insulin glargine was 80%. The majority of the adverse events were mild in severity. A total of 3% subjects withdrew due to adverse events: 4% in the **Levemir**® group, 2% in the NPH insulin group and 4% in the insulin glargine group. The most common adverse events with **Levemir**® were upper respiratory tract infection and headache. For adverse events reported in ≥ 1% of subjects, the only events reported in higher frequency with **Levemir**® than with comparators were injection site disorders, cystitis and hyperhidrosis. No severe adverse events were reported in ≥ 1% of subjects in the **Levemir**® or the NPH insulin groups.

Less Common Clinical Trial Adverse Events (<1%)

In addition, the following adverse events were reported at an incidence of <1% for **Levemir**® and NPH insulin in controlled clinical trials (in more than 1 subject, with higher frequency with **Levemir**® than with NPH insulin), regardless of drug relationship.

Respiratory system disorders: pneumonia, laryngitis, asthma, tracheitis, respiratory disorder and pulmonary edema.

Central and peripheral nervous system disorder: migraine, tremor, hypertonia, neuralgia, dysphonia, hyperkinesia, hyporeflexia, carpal tunnel syndrome, hyperaesthesia and paralysis.

Gastro-intestinal System disorders: gastritis, constipation, tooth disorder, gingivitis, gastro-intestinal disorder (not otherwise specified), haemorrhoids, dry mouth, colitis, gastroesophageal reflux, tooth caries aggravated, dysphagia, rectum hemorrhage, irritable bowel syndrome and mucositis (not otherwise specified).

Body as a whole - general disorders: allergic reaction (anaphylactic shock), potentially allergic reaction, headache, asthenia, hot flushes, syncope, carpal tunnel syndrome, neck rigidity, enlarged abdomen, substernal chest pain, aggravated condition, face edema, mouth edema and sudden death.

Musculo-skeletal system disorders: arthrosis, bone fracture, tendon disorder, back pain, ischias, osteoporosis, tenosynovitis, torticollis and muscle weakness.

Resistance mechanism disorders: abscess, rhinitis, otitis media and parasitic infection.

Vision disorders: abnormal vision, eye pain, eye infection, eye abnormality, keratitis, corneal ulceration, ocular hemorrhage and retinal hemorrhage.

Skin and appendages disorders: skin disorder, pruritus, increased sweating, eczema, skin ulceration, onychomycosis, skin hypertrophy, acne, photosensitivity reaction, dry skin, alopecia, bullous eruption, dermatitis contact, dermatitis, cold clammy skin, lichenoid dermatitis, pilonidal cyst, skin discolouration, otitis externa and verruca.

Secondary terms: other events, bite food poisoning, medication error, varicella and under assessment.

Metabolic and nutritional disorders: hyperglycemia, hypoglycemic coma, hyperlipemia, gout, thirst, weight decrease, aggravated diabetes mellitus, hyperkalaemia, xerophthalmia and diabetic coma.

Application site disorders: injection site hematoma, injection site inflammation, cellulitis and needle injury.

Psychiatric disorders: anxiety, somnolence, confusion, anorexia, emotional lability and thinking abnormally.

Urinary system disorders: renal pain, albuminuria, hematuria, polyuria, abnormal glomerular renal function and abnormal urine.

Cardiovascular disorders, general: cardiac failure, edema dependent, heart murmur, weak pulse, aneurysm, left cardiac failure and heart disorder.

Reproductive disorders, female: dysmenorrhea, vaginitis, menorrhagia, premenstrual tension, amenorrhoea, breast disorder (not otherwise specified) and mastitis.

Platelet, bleeding and clotting disorder: epistaxis, hematoma and arterial leg thrombosis.

Hearing and vestibular disorders: earache, ear disorder (not otherwise specified), motion sickness and vestibular disorder.

Vascular (extracardiac) disorders: phlebitis, flushing, vascular disorder, leg thrombophlebitis, vein disorder and purpura.

Heart rate and rhythm disorders: palpitation, bradycardia and heart block.

Myo-endo-pericardial and valve disorder: angina pectoris, cardiomyopathy and myocardial infarction.

Neoplasm: lipoma, ovarian cyst and lymphoma malignant.

Endocrine disorders: hypothyroidism, hyperthyroidism and goitre.

Red blood cell disorders: hypochromic anaemia.

Liver and biliary system disorders: biliary pain.

White cell and RES disorders: lymphadenopathy.

Special senses other, disorders: taste perversion.

Collagen disorders: rheumatoid arthritis.

Post-Market Adverse Drug Reactions

As of 31 October 2006, Novo Nordisk has received 115 adverse drug reaction reports in paediatric patients. Of these cases, 52 were serious (hereunder 8 unexpected). Most adverse reactions were reported in the following SOCs (System Organ Class): General disorders and administration site conditions, Metabolism and nutrition disorders, Investigations and Skin and subcutaneous tissue disorders (see table 2 below). The nature of the events reported is expected in relation to administration of an insulin product. Furthermore, the type of adverse events in pediatric population is similar to that seen in adults. A higher frequency of hypoglycemia was reported in children compared to adults; however this can be explained by underreporting of these events in adults.

In children aged 6-11 years, 39 cases of adverse drug reactions were reported spontaneously, of which 11 were serious (one of them was unlisted). In children aged 12-17 years, 64 cases of adverse drug reactions were reported, of which 35 were serious (four of them were unexpected).

Twelve (12) cases of spontaneously reported adverse drug reactions occurred were reported in children below 6 years of age and were thus recorded in relation to off-label use – three of these cases were serious.

Table 2 – Distribution of Post-market Adverse Events in Children and Adults by System Organ Class

SOC (System Organ Class)*	General disorders and administration site conditions (most frequent events – injection site reactions)	Metabolism and nutrition disorders (most frequent events – hypoglycemia)	Investigations (most frequent events – Blood Glucose increased)	Skin and subcutaneous tissue disorders (most frequent events – rash, pruritus and urticaria)
Children (<18 years)	29%	27%	12%	12%
Adults	30%	13%	20%	9%

** System Organ Class are coded by use of MedDRA® (Medical Dictionary for Regulatory Affairs

DRUG INTERACTIONS

Overview

Drug Interactions

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

Thiazolidinediones may induce oedema and/or heart failure with higher rates of heart failure when combined with insulin. Therefore, the combination of Insulin with a Thiazolidinedione is not indicated for the treatment of Type 2 Diabetes Mellitus.

The following substances may reduce insulin requirements: Oral antidiabetic drugs, monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, and alcohol. The following substances may increase insulin requirements: Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, beta-sympathomimetics, growth hormone and danazol. Beta-blocking agents may mask the symptoms of hypoglycemia and delay recovery from hypoglycemia. *Octreotide/lanreotide may both increase and decrease insulin requirement.* Alcohol may intensify and prolong the hypoglycemic effect of insulin.

Drug-Drug Interactions Interactions with other drugs have not been established.

Drug-Food Interactions Interactions with food have not been established.

Drug-Herb Interactions Interactions with herbal products have not been established.

Drug-Laboratory Interactions Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia. (Please see **Supplemental Product Information** - HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE)

Administration

Levemir® should not be mixed or diluted with any other insulin for injection (see **Safety Information** - WARNINGS AND PRECAUTIONS).

Levemir® (insulin detemir) is administered subcutaneously in the abdominal wall, the buttock, the thigh or the upper arm. Injection sites should be rotated within the same region. As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. **Levemir**® should never be used if it has become viscous (thickened) or cloudy; it should only be used if it is clear and colourless. **Levemir**® should not be used after its expiration date.

In patients with diabetes mellitus, optimized metabolic control effectively delays the onset and slows the progression of late diabetic complications. Optimized metabolic control, including glucose monitoring is therefore recommended. As a precautionary measure, patients should carry a spare syringe and extra insulin in case the insulin delivery device is lost or damaged.

HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE

Hypoglycemia may occur as a result of an excessive dose of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia. Symptoms of hypoglycemia may occur suddenly. They may include cold sweat, cool pale skin, fatigue, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may be fatal. Mild hypoglycemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that patients with diabetes carry sugar-containing products. Severe hypoglycemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

Product Monograph available on request.

Novo Nordisk Canada Inc. 300-2680 Skymark Avenue, Mississauga, Ontario L4W 5L6 905-629-4222 or 1-800-465-4334. www.novonordisk.ca

PI update: April 2010-04-16

PAAB LEV1520E/05/2010

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

MERCK

Merck Canada Inc., Kirkland, Quebec

JMT-34770160-JA