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Update on Lung Cancer

BOUCHARD AND AGULNIK

**A Systematic Review of Combination
Therapies for Smoking Cessation**

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Lung Cancer: Still a Major Health Issue

Lung cancer remains the leading cause of cancer deaths in Canada. In men, the mortality rate is 47.2 per 100,000, which is more than prostate cancer and colorectal cancer combined.¹ In women, the mortality rate is 35.6 per 100,000, more than breast cancer and colorectal cancer combined. The lifetime risk of developing lung cancer is 8.6% in men and 7.0% in women.¹ But not all persons are at equal risk, as smoking remains the single most important risk factor for the development of lung cancer (as well as for other cancers).²

In this issue of the *CJGIM* there are two articles of relevance to this important health issue. The article by Bouchard and Agulnik summarizes new interventions from lung cancer screening to lung cancer management, fields that have evolved over the past decade. The second article by Nahn and colleagues discusses the therapeutic options that involve combination therapies to assist smokers to quit.

Bouchard and Agulnik discuss the benefits of screening patients at increased risk for lung cancers associated with smoking. Benefits are attained, but not without a considerable consumption of health care resources. An NNT of 327 patients must be screened with low-dose CT scans yearly for three consecutive years (compared to chest X-ray only) to prevent one death from lung cancer. The article also identifies a number of tumour-specific advances in the treatment of late stage cancers, but we are informed that the benefits are limited to 1–5 months of increased life. In the article by Nahn and others, we are first reminded of the rather disappointing success rate for smoking cessation therapies and then, through a systematic review, we see that trying to improve smoking cessation with combination therapies is similarly disappointing.

Overall, these articles might generate a somewhat pessimistic vision for curtailing the morbidity and mortality associated with lung cancer. But to offer some optimism on the subject, mortality has decreased in men over the past two decades, and this has been attributed to the success of campaigns and policies to reduce cigarette smoking. It would appear the best solution to the problem of lung cancer is to prevent individuals from starting to smoke in the first place. While physicians in their encounters with patients can certainly reinforce that message where possible, it will continue to be extremely important that policy makers implement smoking prevention programs that impact the population in the second and third decades of life, when smoking begins. In 2012, the smoking prevalence for Canadians aged 15 years and over was 16.1%,³ so society still has plenty of work to do.

Mitch Levine

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Le cancer du poumon, encore et toujours un problème de santé dévastateur

Le cancer du poumon est toujours la principale cause de décès par cancer au Canada. Chez les hommes, le taux de mortalité est de 47,2 par 100 000, un taux supérieur à ceux du cancer de la prostate et du cancer colorectal réunis¹. Chez les femmes, le taux de mortalité est de 35,6 par 100 000, un taux supérieur à ceux du cancer du sein et du cancer colorectal combinés. Le risque sur une vie entière d'apparition d'un cancer du poumon est de 8,6 % chez l'homme et de 7,0 % chez la femme¹. Mais, le risque n'est pas le même pour tout le monde, car le tabagisme demeure le plus important facteur de risque de cancer du poumon (et d'autres cancers)².

Dans le présent numéro de *La Revue canadienne de médecine interne générale* (RCMIG), deux articles abordent cet important problème de santé. Celui de Bouchard et Agulnik résume les nouvelles interventions dans le dépistage comme dans la prise en charge du cancer du poumon, deux volets qui ont évolué dans la dernière décennie. L'autre article, celui de Nahn et ses collègues, examine les options thérapeutiques sur le plan des traitements combinés favorisant l'abandon du tabac.

Bouchard et Agulnik soupèsent les avantages du dépistage des personnes à risque de cancer du poumon dû au tabagisme. Les avantages sont réels, mais au prix de l'utilisation de ressources sanitaires considérables. Il faut dépister 327 personnes par la tomodensitométrie à faible dose chaque année pendant trois ans consécutifs (comparativement à la radiographie pulmonaire seulement) pour prévenir un décès par cancer du poumon. L'article souligne également certaines percées dans le traitement du cancer aux derniers stades, mais qui ne prolongent la survie que d'un à cinq mois. Dans leur article, Nahn et ses collègues constatent à regret le faible taux de réussite des thérapies de désaccoutumance au tabac (< 5 %) et nous font voir, par l'entremise d'une étude systématique, que les traitements combinés se révèlent peu efficaces dans l'amélioration de ce taux.

En contrepoint à la vision quelque peu pessimiste de ces articles quant à la possibilité de diminuer la morbidité et la mortalité liées au cancer du poumon, mentionnons que la mortalité masculine a diminué dans les 20 dernières années, baisse que nous devons aux campagnes et aux politiques destinées à contrer le tabagisme. Selon toute apparence, la meilleure solution au problème du cancer du poumon est de tuer le tabagisme dans l'œuf, c'est-à-dire faire en sorte que les gens ne commencent pas à fumer. À l'évidence, les médecins doivent continuer de renforcer ce message, néanmoins il est extrêmement important que les décideurs et les responsables des orientations politiques mettent en place des programmes de prévention de l'usage du tabac efficaces chez les jeunes dans la dizaine et la vingtaine, à l'âge où ils commencent à fumer. En 2012 au Canada, la prévalence du tabagisme dans la population âgée de 15 ans ou plus était de 16,1 %³; la société a encore beaucoup à faire à ce chapitre.

Mitch Levine

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3. Santé Canada. Enquête de surveillance de l'usage du tabac au Canada (ESUTC). Ottawa (ON): Santé Canada; 2012.

CSIM Mission Statement

Mission Statement

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

Vision

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

Values

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

Mission

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

Vision

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

Valeurs

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

CSIM Continuing Professional Development Mission Statement

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

Mission de la SCMI sur le plan du développement professionnel continu

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

Acute Care SINS:

Surgical Insights for the Non-surgeon

Chapter 11: Cardiothoracic SINS

Martin Beed DM, R Khadaroo MD PhD, Gurmeet Singh MD, Peter G Brindley MD

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Summary

“Surgical Insights for the Non-surgeon,” or SINS, is composed of several short chapters intended to cover fundamental surgical knowledge for non-surgeons. The authors focus on surgical pearls, operative insights, and applied anatomy. In Chapter 11 of this series, the authors address cardiothoracic surgical issues.

Résumé

L'ouvrage « Surgical Insights for the Non-surgeon » (aperçu de la chirurgie à l'intention du non-chirurgien) se compose de courts chapitres couvrant les connaissances fondamentales en chirurgie. Les auteurs se concentrent sur des enseignements tirés de leur expérience, des aspects opératoires et l'anatomie appliquée.

“To wake the soul by tender strokes of art; To raise the genius, and to mend the heart.”

—Alexander Pope

“How do you know who the cardiac surgeon is at a party? Oh, don't worry, he'll tell you”

—Anonymous

Anatomy

For centuries, the cardiocentric view predominated over the encephalocentric. After all, concluded Aristotle, the body dies when the heart stops; the voice emanates from the lungs; and one can (if so disposed) poke the brain without producing pain. It took centuries (and Galen) to convince us otherwise. It then took until after the Second World War to believe that we could safely operate in this arena. Regardless, poetry and pop-songs prove that the heart and its ailments still hold our attention. What follows is a more prosaic anatomic primer.

Thoracic cavity surgery involves one of three main anatomical areas: 1) the heart, 2) lungs and pleural spaces (including diaphragm and chest wall), and 3) other mediastinal structures (see below). Within the thorax, two lungs are attached to the mediastinum at the hilum (plural is “hila”). It is through these ‘roots’ that the blood vessels and bronchi pass. The lungs are not attached to the thoracic cavity at any other location. Each lung is covered by pleura – the lining which wraps around the lungs and also covers the inside of the thoracic cavity. *Visceral* pleura covers the lung; *parietal* pleura covers the inside of the chest wall, diaphragm, and mediastinum.

The right lung has three lobes (upper, middle and lower), separated by two fissures (oblique and horizontal). The left lung has two major lobes (upper and lower), separated by an oblique fissure. The bronchial tree starts within the mediastinum, and enters each lung through the hilum as right and left main bronchi. Each main bronchus divides into lobar bronchi (corresponding to each lung lobe) before dividing further into segmental bronchi. (Figure 1) Within the left lung lies the lingula (a smaller counterpart to the right middle lobe).

Figure 1. Anatomy of the bronchial tree.

The mediastinum is commonly described in four parts: superior; anterior; middle; posterior (Figure 2). The superior mediastinum contains the inferior trachea, esophagus, thoracic duct, aortic arch, brachiocephalic artery, left carotid and subclavian arteries, brachiocephalic veins, superior vena cava (SVC), phrenic nerve, vagus nerve (and its recurrent laryngeal branch), and lymph nodes. The anterior mediastinum contains the thymus and lymph nodes. The middle mediastinum contains the heart and pericardium, roots of the great vessels, azygous vein arch, lung roots, bronchial lymph nodes, and phrenic nerves. The posterior mediastinum contains the descending aorta, azygous and hemi-azygous vein, esophagus, thoracic duct, vagus and splanchnic nerves.

The chest wall consists of skin, subcutaneous tissues, and muscles: the pectoralis muscles (anteriorly), latissimus dorsi and serratus (postero-laterally), and the sternum (manubrium, body, xiphoid process). There are 12 ribs, with 1-7 considered “true” ribs (or “fixed ribs” or “vertebrosternal ribs”) because they attach directly from vertebra to sternum. Ribs 8-12 are “false ribs” (or “vertebrochondral ribs”): with 8-10 attaching to the sternum indirectly via the costal cartilages of the ribs above. Ribs 11 and 12 (which have cartilaginous tips) are called “floating ribs” because they attach only to the posterior vertebrae, and not to the sternum or sternal cartilage. Ribs 1-7 provide structure and protection; ribs 8-12 allow flexibility and respiratory excursion.

Anyone who has been for barbeque-ribs knows that the intercostal spaces contain layers of muscle. The external intercostals are positioned anterior-to-inferior, and the internal intercostals are posterior-to-inferior. The neurovascular bundle is found between two layers of the

Figure 2. Compartments of the thoracic cavity.

Figure 3. Coronary arteries (anterior view).

internal intercostal and sheltered behind the “blade” of the rib above (therefore place chest tubes above the rib, not below, so as to avoid a bloody mess). God put the internal mammary artery (or internal thoracic artery) near the midline: presumably to give cardiac surgeons easy access to this conduit vessel.

The diaphragm has three muscular leaflets that surround a central tendon. This muscular dome separates the thoracic from abdominal cavity. The diaphragm attaches to the xiphoid process and costal margin anteriorly, and the ribs and vertebrae posteriorly. The right and left crura (aka the posterior diaphragmatic tendons) insert into lumbar vertebrae L1 and L2. The body of the diaphragm has three foramina (windows) that allow passage of the esophagus, descending aorta and inferior vena cava (IVC).

The heart is covered by fibrous pericardium, beneath which the right and left coronary arteries provide myocardial blood supply. The right coronary artery starts above the anterior aortic valve leaflet. It branches to the right atrium and sinoatrial node before dividing into the right marginal (acute marginal) and posterior interventricular arteries (posterolateral branch and posterior descending artery - in patients with right dominant anatomy). The left coronary artery commences above the left posterior aortic valve leaflet and continues as the left ‘main stem’ before dividing into the left anterior descending (which in turn gives rise to diagonal branches) and the circumflex artery (which further divides into obtuse

marginal arteries and the posterior descending artery in left dominant anatomy). There is a variable degree of anastomotic linkage between the distal right and left coronary arteries. (Figure 3)

The heart is divided into right and left sides (referring to the ‘sides’ of the circulation, pulmonary versus systemic, rather than anatomic position). The atria are separated from the ventricles by atrioventricular (AV) valves (tricuspid and mitral). The semilunar valves (aortic and pulmonary) control blood egress from the ventricles. The right atrium can be thought of as an enlarged area within a continuous tube – the upper part of the tube being the SVC, and the lower portion being the IVC. The tricuspid (three-leaflet) valve sits between the right atrium (RA) and ventricle (Figure 4). The right ventricle sits partially on the diaphragm, and partially behind the sternum and anterior ribs (and therefore is the ventricle most commonly initially injured during stabbings). The right ventricle becomes the pulmonary trunk near its superior surface at the position of the trileaflet pulmonary valve. The left atrium, which collects blood from the pulmonary veins, sits almost beneath the carina of the bronchi (hence, when enlarged, it can cause “splaying” of the carina on chest Xray).

Functioning heart valves ensure unidirectional blood flow. The mitral is the only valve that normally has two leaflets. These leaflets, when together, resemble a Bishop’s hat : a mitre. After oxygenated blood passes through the mitral valve it enters the left ventricle, which sits to the left and partly

4. Anterior cardiac view with cutaway demonstrating valve and papillary muscles.

behind the right ventricle. The left ventricle is far more muscular than the right (hence the larger troponin increase with left-sided versus right-sided damage). In 2D short-axis echocardiography, the left looks like a thick-walled donut, whereas the right is thin and D-shaped. The left ventricular outflow tract contains the aortic valve (three leaflets normally; bicuspid occasionally- which can result in pathology) and the aortic root. Within both ventricles are papillary muscles, which anchor the AV valves in place. (Figure 4). The contraction of the muscle fibers of the heart is normally synchronized, however when the individual small fibers (or fibrilla, in Latin) start to contract independently of one another, the heart is said to fibrillate.

Cardiothoracic Incisions

Access to the thoracic cavity is obtained by:

- Median sternotomy
 - Sternum is split and the ribcage spread apart
 - Typically reserved for cardiac (a.k.a. open-heart) surgery
 - Or complex anterior thoracic surgery
 - E.g. excision of a massive retrosternal goiter
 - *This hurts a lot*
- Lateral and posterolateral thoracotomy
 - Incision made in an intercostal space
 - Ribs “spread” apart, or partially resected
 - *This hurts a lot, too*

- Partial (or minimally invasive) sternotomy
 - There are upper and lower variations
 - Choice is based upon optimal surgical site access
 - *This hurts less*
- Keyhole intercostal incisions
 - Providing space to insert an endoscope
 - Minimally invasive: video-assisted thoracotomy (VATS)
 - *This hurts least*

Lung Resection Surgery

- Most commonly for cancer
 - Sometimes for bullae or infections
 - E.g. chronic suppurative diseases or aspergilloma
- Requires pre-op assessment of respiratory reserve
 - Ventilation-perfusion lung mapping
 - To ensure patients can cope following resection
 - Ideally, the recommended residual postoperative FEV₁ is > 1.5L for lobectomy and > 2L for pneumonectomy
 - Each lobe provides approximately 1/5 of lung capacity (if healthy)
 - But may contribute less if already diseased
 - Therefore, bad lungs aren’t missed!
- Lung resection options
 - Resection of a lobe (lobectomy)
 - Resection of part of a lobe (partial lobectomy or wedge resection)

- Resection (rarely) of an entire lung (pneumonectomy)
- With carinal disease, a “sleeve pneumonectomy” may be performed
 - Resect the diseased lung and its bronchus
 - Reattach the good lung back to the trachea
- Can disrupt post-op lymphatic drainage/ciliary flow
- Lung volume reduction surgery (LVRS)
 - For severe hyperinflation in emphysema
 - Technically, similar to other lung resection surgery
 - But the aim is to remove the least functional part of the lung
 - And preserve cardiovascular flow in and preserve airflow out
- Complications of lung resection surgery include:
 - Pain
 - Respiratory failure
 - Especially in patients with frailty/extensive lung disease
 - Pneumonia and sepsis
 - Especially with pre-existing abscess
 - Or if infected secretions were trapped distally
 - Dysrhythmias
 - Especially atrial fibrillation (AF)
 - AF is also associated with post-op pneumonia or mediastinitis
 - Persistent pneumothorax, and bronchopleural fistulae (air leaks) (see below)
 - Hemorrhage and hemothorax
 - Pulmonary embolus (far less common than pneumonia)

Chest (a.k.a Pleural) Drains

- Common on both surgical and medical wards
- Multiple drains may be placed during thoracic surgery
 - Typically, one is placed apically
 - To drain pneumothoraces
 - Another is basal, or next to the resected area
 - To drain blood or effusion
 - Occasionally, contralateral drains are placed
 - These can pass *over* the mediastinum
 - To the uninitiated, the Xray can look as if tubes pass *through* the heart
- There are many potential complications of chest drain insertion, including:
 - Hemorrhage
 - Trauma to the lung, pericardium, or mediastinal structures
 - Never insert a surgical chest drain using a trocar
 - Never do that – trocars are sharp and will easily penetrate heart and other structures.
 - Migration or misplacement of tubes
 - In the obese it is common to misplace into subcutaneous tissues rather than the thoracic cavity
 - Chest tube drainage holes can migrate until they are outside the patient
 - Which loses the airtight seal, and can entrain air
 - Damage to the diaphragm or abdominal viscera
 - More common when drains are outside of the “safe zone”
 - The safe zone is:
 - Superior to the nipple; inferior to the axilla; lateral border of pectoralis major, anterior border of latissimus dorsi)
 - Insertion advice:
 - In women: follow the infra-mammary crease to the mid axillary line
 - In men: follow the nipple line laterally to the mid axillary line
 - Accidental trans-diaphragmatic chest drains
 - The chest drain goes through abdominal structures (such as liver) before entering the thoracic cavity
 - More common when using Seldinger insertion kits, or when not using ultrasound
- Persistent bleeds may require surgical exploration (see surgical pearl)
- Persistent pneumothoraces may indicate a bronchopleural fistula
 - Chest drains may need to be on suction to encourage drainage (typically minus 20cmH₂O)
 - Later, you may need to decrease that suction to allow hole to heal
 - Or a second chest drain may be required
 - Which is usually placed in a different position
- Maintain an index of suspicion regarding occult pneumothoraces
 - Especially in patients on positive pressure ventilation
 - On supine Xrays, pneumothoraces may not be visible apically
 - Air collects anteriorly, so look for:
 - Abnormally deep costophrenic or cardiophrenic recess
 - Sharp cardiomedial border or pneumomediastinum
 - “Double diaphragm” sign outlining inferior lobes
 - Air ‘bands’ in the minor fissures

- Depressed ipsilateral diaphragm
- May require lateral Xray or CT
 - But beware the “donut of death” (a.k.a. the CT scanner!)
 - Only send for imaging if stable
 - Radiation never cures a pneumothorax but it can endanger a patient
- Rarely clamp chest drains
 - It may result in tension pneumothorax
 - However, after pneumonectomy, tubes may require a ‘clamp and release’ protocol
 - This encourages fluid to collect in the resected hemithorax
 - Which may decrease post-pneumonectomy syndrome
 - A mediastinal shift that compresses/ stretches the tracheobronchus/esophagus
 - Resulting in shortness of breath, dysphagia, or heartburn
- Perform a chest Xray after all chest drain insertions
 - Including chest drains placed during surgery

Surgical Pearl:

Hemorrhage from chest drains:

- The commonest causes of bleeding are:
 - Intercostal vessel damage (e.g. during scalpel incision, or laceration during drain insertion)
 - Intraparenchymal damage (e.g. during drain insertion)
 - Damage to associated tissues (e.g. trans-diaphragmatic insertion)
- Anything that results in ≥ 600 mls in 6 hours requires surgical review, e.g.
 - 600 mls in one go
 - 200 mls/hour for 3 hours
 - 100 mls/hour for 6 hours
- If bleeding is suspected, obtain an urgent chest Xray and/ or ultrasound
 - Ultrasound (U/S) good for detecting fluid within the thoracic cavity (and may visualize fibrin-stranding associated with hemorrhage)
 - U/S not good for seeing through adipose (i.e. obese patients) or air (e.g. pneumothorax/surgical emphysema)
 - Hemorrhage may be occult/invisible (i.e. the chest drain may be blocked)
- No absolute indications for surgery
 - Instead, respond to the patient’s condition

Pleural And Chest Wall Surgery

- Pleurectomy
 - Performed for recurrent pneumothoraces
 - Complication = hemorrhage
- Decortication
 - Literally, resection of an outer layer
 - Performed for mesothelioma or organized empyema
 - Complications include hemorrhage or septic “shower” during/after surgery
- Chest wall surgery
 - Most often for lesions involving ribs or intercostal muscles
 - Rib fixation is becoming more common following traumatic flail-chest
 - Severe pectus excavatum (in-drawn, or dish-shaped chest)
 - Open repair (Ravitch procedure), or
 - Minimally invasive repair with a metal bar (Nuss procedure)

Pain after thoracic surgery or thoracic trauma

- Thoracotomy incisions can be very painful
- As with all incisions, movement (in this case, breathing) exacerbates pain
- Pain can lead to shallow breathing
 - Which in turn leads to lung atelectasis and retention of secretions
 - Which in turn leads to respiratory failure
- Physiotherapy and early mobilization are very beneficial
- Good analgesia also important
 - As a *minimum*, patients should cough and deep-breathe
 - Better still if they can mobilize, and engage with physio
- Analgesia depends upon patient’s characteristics, and staff skill,
 - Options include:
 - Epidural infusions or paravertebral infusions
 - Requires experience to insert, trouble-shoot and monitor
 - Watch for hypotension: due to sympathetic blockade
 - Systemic opiates
 - Given as infusions, boluses, or patient-controlled (PCA)
 - Watch for sedation and respiratory depression
- Pneumonia is a common complication of thoracic injuries or surgery
 - Antibiotics should cover hospital-acquired bugs and aspiration
- Chronic, neuropathic pain can be associated with chest trauma and surgery

Figure 5. Esophageal resection with gastric pull-up. The stomach replaces the esophagus .

Figure 6. Chest radiograph after an esophagectomy.

Esophageal Resection (Figure 5)

- Performed for esophageal disease
 - e.g. cancer or benign strictures
 - e.g. leaks or trauma (i.e. drinking bleach; iatrogenic perforation)
- Common techniques include:
 - Ivor Lewis approach (for distal esophageal tumors)
 - Involves a right thoracotomy and an upper midline incision
 - McKeown's approach (for proximal esophageal tumors)
 - Involves a right thoracotomy and a neck incision
 - Trans-diaphragmatic approach
 - Transhiatal rather than transthoracic
 - Mobilization of the esophagus, and stomach
 - With a 'pull-through' the diaphragm (so no thoracotomy is performed)
- Resulting esophageal "conduit" can have tenuous blood supply
 - Prone to anastomotic breakdowns and mediastinitis
- Complications:
 - Similar to lung resection surgery
 - Also chyle leaks

- Fatty fluid, from the lymphatics/thoracic duct in the thorax
- As well as chest drains, a naso-gastric (NG) tube often left as an endo-luminal drain after surgery (Figure 6)
 - Placed at the level of the anastomosis
 - Therefore, on Xray, it may seem 'malpositioned'
 - I.E. it sits above the diaphragm
 - Do not manipulate the NG tube
- Esophageal surgery is mediastinal surgery
 - Therefore, effusions/hemorrhage can be contralateral to the thoracic incision
- Rarely, esophageal tumours can adhere to the pericardium
 - Cardiac complications, such as tamponade, can occur

Surgical Pearl:

Esophageal leaks and ruptures

Causes include:

- Esophageal cancer
- Trauma/iatrogenic perforation (e.g. during endoscopy, trans-esophageal echocardiography, dilatation of an esophageal stricture)
- Spontaneous esophageal rupture
 - Boerhaave's syndrome (associated with vomiting – patients often describe a “popping” feeling).
 - Perforation of esophageal erosions, or an infected ulcer (typically HIV-related)
 - Ingestion of corrosive substances, or ‘pill-esophagitis’

Esophageal rupture/leak associated with:

- History of sustained vomiting, dysphagia, odynophagia
- Unexplained chest pain, occasionally radiating to the left shoulder
- Unexplained surgical emphysema, pneumothorax or pneumomediastinum – especially if pneumothorax persists despite adequate drainage
- Grossly contaminated pleural fluid (often with particulate matter)
- Enteric organisms in the pleural fluid (particularly mixed flora, enterococcus, or candida)

Diagnosis often delayed due to differential diagnosis:

- Pneumonia/lung abscess
- Myocardial infarction
- Spontaneous pneumothorax
- Pancreatitis
- Pericarditis

Treatment: i) Adequate chest drainage (often a large bore drain due to particulate matter), ii) Broad-spectrum antibiotics (due to the organisms mentioned above), iii) Early surgical consultation

Other considerations

Fluid balance after surgery and thoracic trauma

- Lung vascular permeability is increased
- Restricting intravenous fluids can reduce interstitial edema ('dry lungs are happy lungs')
 - Approximately 1-1.5 ml/kg/hour
 - But, must be balanced against the need for intravascular resuscitation

Coronary Revascularization Surgery

- Coronary artery bypass grafting (CABG)
 - To circumvent (i.e. bypass) stenotic coronary arteries in critical ischemic heart disease
 - Increasingly, first line therapy is percutaneous coronary intervention (PCI)
 - CABG is preferred for:
 - Multi-vessel disease
 - Left main stem disease
 - Mild-moderate left ventricular dysfunction (ejection fraction 35-50%) and either multi-vessel disease or proximal LAD disease
 - Diabetic with multi-vessel disease
 - Complex three-vessel coronary artery disease
 - Possibly also chronic kidney disease
- Options for conduit include:
 - Saphenous vein; radial artery; left internal mammary artery (LIMA) (also referred to as left internal thoracic artery (LITA))
- Typically patients mechanically ventilated for a short period after surgery
 - Early post-op care performed in an intensive care unit (ICU)
 - Median sternotomies not usually as painful as other thoracotomies (unless, one is the actual recipient of the sternotomy incision, in which case, it still hurts like heck)
 - So, less analgesia required; ventilator weaning usually rapid
- Complications include:
 - Myocardial infarction (MI)
 - Leading cause of death post-CABG; increased subsequent incidence of heart failure and hospital readmission

- Approximately 1-in-30 patients have a perioperative MI
 - Increased MI risk persists for approximately 30 days
 - Some need lengthier mechanical circulatory support
 - Intra-aortic balloon counter pulsation devices (IABP) or ventricular assist devices may be inserted with surgery
- Low Cardiac Output Syndrome
 - Inadequate cardiac output/end-organ oxygen delivery
 - Reduced myocardial performance (systolic dysfunction) (RV, LV, or both) or diastolic dysfunction
- Cardiac dysrhythmias
 - Most commonly AF
 - More malignant rhythms too (ventricular tachycardia, etc)
 - Intraoperative temporary epicardial pacing leads are commonly placed
 - These allow for post-operative cardiac pacing
- Adverse cerebral outcomes
 - Of varying severity, but affects approximately 6%
 - Full stroke in 1 - 4%
 - Up to 50% of patients may experience delirium
 - Many also suffer post-operative cognitive deterioration/decline
 - A.K.A. “post-perfusion syndrome” / “pump head” (due to its association with cardiopulmonary bypass, CPB)
 - Contributory factors: pre-existing cerebral vascular disease, peripheral vascular disease, age, duration of CPB, smoking, diabetes, renal failure, use of deep hypothermic circulatory arrest
 - Peri-operative emboli from the aorta (atherosclerosis, plaque disruption from aortic cross-clamp application/manipulation)
 - Also air-emboli; debris; micro emboli (fibrin, etc.)
- Decreased renal function
 - Approximately one-third of patients
 - Varying severity
 - Some patients require post-operative dialysis
 - Multifactorial etiology
 - Pre-renal (most often); renal and post-renal (less often)
- Infection
 - Affecting the sternotomy wound, or donor graft sites
 - Look for incisional drainage; erythematous, excessively warm wound and a ‘sternal click’ (i.e. sternal instability)
- Hemorrhage
 - Peri-operative bleeding can lead to tamponade

- Always have a high index of suspicion - ‘it’s tamponade until proven otherwise’
- Central venous pressure (CVP) may NOT be elevated - caval compression from clot can prevent SVC/RA distension
- Look out for oliguria, elevated lactate, and other signs of low cardiac output syndrome
- BEWARE: anticoagulation is required for cardiopulmonary bypass
 - Risk of bleeding increased if inadequately reversed after surgery
 - Coagulopathy is common after cardiac surgery (heparin ‘rebound’, fibrinolysis)

Surgical Pearl:

Cardiac arrest after cardiac surgery

- Epinephrine (adrenaline) to be used with extreme caution and probably reduced dose – to reduce hemorrhage and ischemia.
- Epicardial pacing helps if asystole or severe bradycardia
- Re-open the sternotomy early (even if tamponade not clinically obvious)

In some centers, different guideline are used for arrests following cardiac surgery (these guidelines differ from the AHA/ACC guidelines – and are called cardiac advanced life support or CALS)

Cardiopulmonary bypass (CPB)

- Most cardiac surgery is performed using CPB (heart-lung machine)
- CPB maintains systemic circulation by isolating/excluding heart and lungs
- The heart is arrested to facilitate a motionless, bloodless, surgical field
 - Usually achieved by infusing a cold, potassium-containing, cardioplegia solution: directly into the aortic root or coronary ostia
 - After surgery, the heart is restarted and the patient weaned from CPB
 - Less commonly, surgery can be performed “off-pump”
 - This uses a stabilization system which typically means a specialized retractor or suction cup system (intended to reduce the motion of the target cardiac wall)
 - Allows surgery while the heart is still beating
- Prior to arresting the heart, patient is cannulated and connected to an extracorporeal circuit, consisting of:

- A venous reservoir to drain blood under gravity from the venous system (right atrium and IVC via a single cannula; or bicaval drainage using two cannulae)
- Blood tubing circuit and roller pump
- Heat exchanger
- Oxygenator and carbon dioxide removal membrane
- Filter to remove air and clot.
- Cardioplegia delivery system.
- Return arterial line to deliver blood
 - Typically returned to the ascending aorta
- Circuits need to be primed (air-removed) prior to use
 - Most commonly primed with crystalloid/colloid solutions in adults
 - Can result in hemodilution (which may offer some rheological advantages to the microcirculation)
- Blood needs to be anticoagulated during CPB
 - Typically with unfractionated heparin
 - Reversed with protamine
 - Heparin-rebound and bleeding can occur
- CPB may cause a systemic inflammatory response
 - This can persist after surgery

Surgical Pearl:

Extra Corporeal Membrane Oxygenation (ECMO)

- a.k.a. bedside CPB

- Principles are similar to CPB
- But specifically refers to use in ICU for prolonged support when conventional hemodynamic and/or ventilatory support has failed
 - Venovenous (VV) ECMO - respiratory support only; preferred when only lung support is required
 - Single cannula (Right Internal Jugular, IJ); or
 - Dual or triple cannula (IJ, femoral vein, femoral vein)
 - Venoarterial (VA) ECMO - cardiac and respiratory support
 - Central cannulation (axillary artery or aorta directly; and right atrium)
 - Peripheral cannulation (usually femoral artery/femoral vein)

Aortic Surgery - Aneurysm And Dissection

- Thoracic aortic aneurysms can be caused by:
 - Hypertension
 - Atherosclerosis
 - Connective tissue disorders (e.g. Ehlers-Danlos or Marfan's syndrome, annuloaortic ectasia)

- Infection/inflammation (e.g. vasculitis secondary to giant cell arteritis, Takayasu's arteritis, rheumatoid arthritis, syphilitic aortitis)
- High-velocity blunt thoracic trauma
- High-intensity weight lifting
- Classification - most useful clinically is the Stanford system:
 - Type A - involves the ascending aorta, regardless of the site of the intimal tear
 - Type B - all other dissections
- Aortic Dissection is a high-mortality, vascular catastrophe.
- Unfortunately, aneurysms typically asymptomatic unless they suddenly leak, rupture, or dilate; at which point: at which point:
 - Chest pain is common (often mistaken for MI)
 - Sharp, tearing chest pain
 - Typically, anterior chest pain in Type A
 - Typically, back pain in Type B - radiates to between the shoulder blades
- For patients with chest pain, always ask: '*why is this not an aortic dissection?*'
 - Because administering thrombolytics can be fatal
 - And because EKG changes can also occur with aneurysms
 - Due to coronary involvement
 - Look for tachycardia, nausea, and a feeling of "impending doom"
 - Admittedly, this latter symptom sounds trite
 - Anecdotally, however, it is surprisingly common
 - Less common signs include:
 - Dysphagia
 - Hoarseness, or occasionally stridor
 - Neck swelling
 - Stroke
- Presentation can also include:
 - Coronary dissection (hence the EKG changes)
 - Rupture/cardiac tamponade
 - Malperfusion syndromes (mesenteric ischemia, limb ischemia, neurologic deficit)
- Surgery usually required for ruptured/leaking aneurysms
 - And considered for subclinical aneurysms ≥ 6 cm
 - Descending aorta aneurysms may be amenable to intravascular stenting
 - Either way, time is of the essence: rapid diagnosis and intervention essential

Aortic Transection/Blunt Aortic Injury

- High-velocity blunt chest trauma with rapid deceleration

- Typically distal to left-subclavian artery (aortic isthmus)
- CXR findings:
 - Left apical cap (pleural blood superior to left lung)
 - Widened mediastinum
 - Hazy aortic knob
 - Left hemothorax
 - Left main stem bronchus displaced
 - Nasogastric tube deviated towards right
 - Tracheal deviation towards right
 - Right mainstem bronchus deviation downwards
 - Widened left paravertebral stripe
- Diagnosis: chest CT angiogram
- Injury classification
 - Type I: Intimal tear
 - Type II: Intramural hematoma
 - Type III: Pseudoaneurysm
 - Type IV: Rupture
- Type I treated medically
- Type II-IV repaired with stenting or surgery
- Increasingly, endovascular (a.k.a. stenting) repair is performed, reducing need for open thoracic repair via thoracotomy
- You can commonly delay that repair if the patient is hemodynamically-stable
 - Without increased risk of rupture

Complications of aortic surgery:

- Includes all of those mentioned following CABG surgery, and also:
- Graft infection
 - Complex problem! Reoperation is high risk!
 - Especially if an aorto-enteric fistula occurs
 - e.g. an anastomotic leak after esophagectomy with aortic inflammation/rupture
- Paralysis (paraplegia)
 - Occurs in descending thoracic aortic surgery (3-4%)
 - Because the aorta provides direct blood supply to the spinal column via segmental arteries
 - Artery of Adamkiewicz is the largest segmental artery (although substantial anatomic variability)
 - Intercostal artery re-implantation and lumbar CSF drainage may be protective- but it is often too late!
- Vocal cord paralysis possible with aortic arch surgery (left recurrent laryngeal nerve injury/transection)
- Death
 - 5-10% die after aortic graft surgery
 - Type A aortic dissection mortality risk is 30%

Valve Surgery

- Valves may be repaired or replaced for failure (regurgitation, stenosis, or infection)
- Most common causes of failure (based upon valve) is:
 - Chronic calcification and degeneration (aortic valve)
 - Chronic rheumatic disease (mitral and aortic valves)
 - Myxomatous disease (mitral valve)
- Systemic causes include
 - Carcinoid syndrome or infectious endocarditis
 - Mechanical failures (e.g. dilatation or papillary muscle rupture)
 - Tricuspid valve infections are most common in intravenous drug users
- Valves can be replaced with tissue (biologic) or mechanical (pyrolytic carbon):
 - Tissue: bovine pericardial, porcine or cadaveric human (homograft)
 - Homograft useful for extensive aortic valve endocarditis with root abscess/significant tissue destruction
 - Mechanical
 - Require life-long anticoagulation (typically acetylsalicylic acid and warfarin)
 - Most common is a bileaflet tilting disc design
 - “Tissue” valves typically last 10-15 years - generally less in younger patients
- Trans-catheter aortic valve implantation/replacement (TAVI/TAVR); balloon aortic valvuloplasty (BAV)
 - An option for frailer patients
 - BUT given its new-ness there is less experience
 - TAVI/TAVR
 - Transfemoral or transapical approach
 - Minimally invasive: less anesthesia; less recovery time
- Complications of valve surgery mirror those following CABG surgery, but also include:
 - Early valve failure
 - Hematoma or suture dehiscence
 - Perivalvular leak
 - Infective endocarditis
 - Both early or late
 - Persistent anatomical disruption of the valve
 - I.e. Annular dilatation of the aortic root
 - Resulting in valve insufficiency
 - Death
 - Approximately 1-in-50 mortality risk after aortic valve surgery

Surgical Pearl:

Native valve endocarditis - indications for consideration of early surgery

- Congestive heart failure from severe aortic/mitral valve regurgitation, or obstruction by vegetation
- Severe pulmonary hypertension
- Paravalvular abscess, fistula tract formation, heart-block
- Recurrent embolism of vegetations
- Vegetations likely to embolize (i.e. >15mm, or >10mm with at least 1 embolic event)
- Transient ischemic attack or stroke
 - Conversely, cerebral haemorrhage leads to surgical delay: because of the risk of further hemorrhage (due to anticoagulation for surgery)
- Relapsing or persistent systemic sepsis (prolonged fever / bacteremia > 7 days)
- Sepsis caused by aggressive or resistant organisms (e.g. *S. Aureus*, meticillin resistant *S. Aureus*, *Brucella*, *S. Lugdunensis*, *Pseudomonas aeruginosa*, Q fever, vancomycin resistant enterococci, fungi)

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Update on Lung Cancer

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Summary

Investigation and treatment of lung cancer has changed dramatically since the last articles in this journal in 2008. These changes include a new study on lung cancer staging, a new tumour, node, metastasis (TNM) classification, linear endoscopic ultrasound as a first-line test for mediastinal staging, investigation and follow-up of ground glass and mixed-lung nodules, radiosurgery for inoperable patients with localized lung tumours, and molecular tests and targeted therapies for advanced non-small cell lung cancer.

Résumé

L'investigation et le traitement du cancer du poumon ont énormément évolué depuis les derniers articles sur le sujet parus dans cette revue en 2008. Ont contribué à cette évolution une nouvelle étude sur la stadification du cancer du poumon, une nouvelle classification TNM, l'échoendoscopie devenue l'examen de première intention dans la stadification médiastinale, l'investigation et le suivi du nodule en verre dépoli et du nodule mixte, la radiochirurgie chez le patient inopérable dont les tumeurs sont localisées et les analyses moléculaires et les traitements ciblés dans le cancer du poumon non à petites cellules de stade avancé.

Screening

According to the 2014 statistics for Canada, lung cancer is still the leading cause of cancer-related deaths and has the second highest incidence, with approximately 26,000 new diagnoses. A major American study (National Lung Screening Trial¹ [NLST]) that included more than 50,000 patients was published in 2011. It showed a decrease in lung cancer mortality of 20% and all-cause mortality of 6.7%. A total of 320 patients had to be screened to save one death by lung cancer. A low-dose computerized axial tomography (CT) scan was done yearly for three consecutive years and compared to a chest X-ray only. Inclusion criteria were age between 55 and 74 years and smoking history of at least 30 pack-years (number of packs of cigarettes smoked per day divided by the number of years the person has smoked). Patients were either still smoking or had stopped in the last 15 years. Since that publication, many medical associations (American Cancer Society of Clinical Oncology [ASC], Cancer Care Ontario, and US Preventive Services Task Force [USPSTF]) have recommended lung cancer screening. However, lung cancer screening is still not a standard of care in the country, due to remaining questions regarding false positives, frequency or length of screening after three years, and concerns about the cumulative risk of radiation. There is also a risk of over-diagnosis related to a subtype of adenocarcinomas, which used to be called bronchioloalveolar carcinoma.

If screening is proposed to a given patient, benefits and risks should be discussed before asking for a computed tomography (CT) scan. The Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) being done in Europe will help to answer these questions, and its results should be available in 2016.

Diagnosis and Staging

Histological Classification and Staging

The seventh tumour, node, metastasis (TNM) classification on lung cancer was published in 2009² due to the prognostic impact on survival (Table 1). It includes both small cell and non-small cell lung cancers. Small cell lung cancers are no longer classified as limited or extensive.

A stage I lung cancer is a tumour less than 5 cm without metastasis in lymph nodes. A stage II is a tumour larger than 5 cm or that invades certain adjacent structures, or a small tumour with metastatic lymph nodes either in the hilum, interlobar region, or lung. A stage III is a tumour that invades a central organ (such as the heart, big vessels, trachea, or oesophagus) or metastatic lymph nodes in the mediastinum, scalene, or supraclavicular region. A stage IV invades pleura or pericardial

Table 1. Descriptors, Proposed T and M Categories, and Proposed Stage Groupings

Sixth Edition T/M Descriptor	T/M	N0	N1	N2	N3
T1 (<2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2–3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (<5 cm)	T1a	IB	IIA	IIIA	IIIB
T2 (>5–7 cm)	T1b	IIA	IIIB	IIIA	IIIB
T2 (>7 cm)	T3	IIIB	IIIA	IIIA	IIIB
T3 invasion		IIIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	T4	IIIB	IIIA	IIIA	IIIB
T4 (extension)		IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral lung)		IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV
Cells in bold indicate a change from the sixth edition for a particular TNM category.					

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Table 2. IASLC/ATS/ERS Classification of Lung Adenocarcinoma in Resection Specimens

Preinvasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma in situ (<3 cm formerly BAC)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Minimally invasive adenocarcinoma (<3 cm lepidic predominant tumor with <5 mm invasion)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Invasive adenocarcinoma
Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
Acinar predominant
Papillary predominant
Micropapillary predominant
Solid predominant with mucin production
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma (formerly mucinous BAC)
Colloid
Fetal (low and high grade)
Enteric

BAC, bronchioloalveolar carcinoma; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society.

effusion or metastases in the other lung or distal organs. Useful resources for information include the staging lung cancer website³ (Figure 1) and the IASLC Staging Atlas application.⁴

In 2011, a new adenocarcinoma classification was published.⁵ The term “bronchioalveolar carcinoma” should not be used anymore (Table 2). Non-mucinous bronchioalveolar carcinomas are now classified as being either in situ, minimally

invasive, or lepidic predominant, based on their size and invasive component. They usually are ground glass lesions on CT scan and have an excellent prognosis after curative surgery. Mucinous bronchioalveolar carcinomas should now be called invasive mucinous adenocarcinomas and they are more often associated with consolidations and are multifocal/multilobar.

Noguchi 1995	IASLC/ATS/ERS 2011	Main CT features
	AAH	GGN
A, localized BAC	AIS	GGN
B, localized BAC with alveolar collapse		GGN/PSN
C, localized BAC with active fibroblastic proliferation	MIA	GGN/PSN
	Lepidic predominant adenocarcinoma (nonmucinous)	PSN SN
	Invasive mucinous adenocarcinoma	PSN with ↑↑ solid component SN Consolidation
D = poorly differentiated E = tubular F = papillary tumor	Invasive adenocarcinoma, classified by the predominant subtype	SN or PSN with ↑↑↑ solid component

Figure 1. Correlation of the new IASLC/ATS/ERS lung adenocarcinoma classification with the Noguchi classification and the corresponding most common computed tomography features of each subtype of adenocarcinoma. The arrow indicates increased solid attenuation and decreased prognosis as the lesions become more invasive on histology. AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; ATS, American Thoracic Society; BAC, bronchioalveolar carcinoma; CT, computed tomography; ERS, European Respiratory Society; GGN, ground-glass nodule; IASLC, International Association for the Study of Lung Cancer; MIA, minimally invasive adenocarcinoma; PSN, part-solid nodule; SN, solid nodule.

Subsolid pulmonary nodules: imaging evaluation and strategic management. Copyright: www.co-pulmonarymedicine.com, 2012, Vol.18, No. 4, p.307. Reprinted with permission.

In 2013, new recommendations were developed regarding investigation and follow-up of subsolid lesions⁶ (subsolid lesions include both ground glass and partially solid lesions). They are generally more grey than white on CT scan images. Partially solid nodules include a ground glass part and a solid part (which means a grey zone and a white zone; this white zone is usually the invasive part, which is solid). These subsolid lesions have a slower growth than a lung cancer with a solid nodule and have a better prognosis. They often correlate with an adenocarcinoma diagnosis on the pathology report. Their investigation will be discussed in the treatment part of this article.

Investigation

A chest CT scan with intravenous contrast should be prescribed for every patient.⁷ If a curative treatment is considered (stages I to III), a positron emission tomography (PET) scan should be ordered, if available. Otherwise, a chest CT scan up to the adrenal glands and a bone scintigraphy should be prescribed to complete extrathoracic staging. For small cell lung cancer, a PET scan could be ordered for stage I to III, but data are more controversial. A PET scan does not adequately evaluate brain or distal limbs. Brain staging (CT scan or, preferably, a magnetic resonance imaging) should be done if there are neurologic symptoms and for every small cell lung cancer. It

should be considered for non-metastatic non-small cell lung cancer, especially for stage III.

For non-small cell lung cancer, the most advanced histological stage should be determined to increase the patient's chances of being cured, unless there are significant risks with the procedure. This is especially important if there is only one site that is suspect of metastases, or if there is no extensive infiltration of the mediastinum. However, for small cell lung cancer, the less invasive test will be done. The whole investigation period should overlap and not be done in a sequential order, to shorten the time of the investigation.

Many studies have confirmed that endobronchial ultrasound (EBUS) combined or not with esophageal ultrasound (EUS) is the first choice to stage hilar or mediastinal lymph nodes that are increased in size on CT scan (smallest diameter at least 1 cm) and/or that are positive on PET scan. If the tumour is central, a mediastinal staging should also be done. If clinical suspicion of lymph node metastasis remains after a negative ultrasound puncture, a surgical staging should be done (mediastinoscopy, mediastinotomy, or thoracoscopy).

If there is a mediastinal metastasis, usual bronchoscopy, or transthoracic, biopsy of the lung lesion is not indicated. EBUS +/- EUS will simultaneously provide the diagnosis and establish the stage.

Solid nodules larger than 8 mm should be considered neoplastic until proven otherwise. Bronchoscopy and transthoracic biopsy (TTB) have high false-negative results. For central lesions, bronchoscopy is diagnostic in about 90% of cases, but only in 20% of peripheral lesions. Regarding TTB, the false-negative rate is 20%. One negative TTB should not exclude a lung cancer diagnosis if the clinical suspicion remains high. Two choices are then offered, either a second TTB or a diagnostic thoracic surgery. Radial EBUS is a new procedure allowing better sampling of a lung nodule than conventional bronchoscopy. The sample is taken under direct ultrasound guidance. This technique is still not widely available and will not replace transthoracic biopsy because the nodule can be too far to be reached with a radial EBUS. Being able to see a bronchus near the nodule improves the diagnostic yield of radial EBUS, with a sensitivity of 80%.

If lung nodules are smaller than 8 mm, they should be called micronodules and be followed by chest CT scan according to cancer risk and their size. Fleischner Society guidelines⁸ are useful to decide the length between follow-up CT scans, to a total follow-up duration of two years. Subsolid nodules (ground glass or mixed solid and ground glass) should

be followed in a different way. Guidelines are not standardized for these lesions. Generally, it is important to remember that lung cancer risk is higher for mixed nodules and that annual CT scan follow-up should be longer (3–5 years) than for solid nodules, in order to be more confident about their benign pattern. Also, a first CT scan should be done after three months to know if the lesion has disappeared, because this is more common with subsolid lesions.

If a subsolid nodule increases in size or develops a solid component, a diagnostic procedure must be done. If nodules are larger than 10 mm, and particularly 15 mm, then a diagnostic procedure is also indicated. The size of the solid component (5 mm or more) of a mixed nodule should also be considered in the decision to further investigate the lesion. One must remember that the rate of false negative PET scans and transthoracic biopsies is greater in subsolid nodules than it is in solid nodules.

Because of the impact on therapies for stage IV non-small cell cancers, the histology (adenocarcinoma, squamous cell carcinoma) should be analyzed using immunohistochemistry, if possible. Generally, two markers are used. These markers are TTF1 and p63 (or p40), respectively, markers for adenocarcinoma and squamous cell cancer. There should be enough tissue for molecular tests to be done ultimately if the diagnosis is an adenocarcinoma. A search for mutations in the epidermal growth factor receptor (EGFR) gene and rearrangement of the anaplastic lymphoma kinase (ALK) gene is requested for adenocarcinoma tumours.⁹ This will be further discussed in the section on therapy.

For pleural effusions in which cancer is suspected, a pleural tap is often obtained. A chest ultrasound will increase the diagnostic yield and decrease the frequency of complications such as pneumothoraces. Chest ultrasound is recommended to localize the site for thoracentesis. If two thoracenteses are negative and the clinical suspicion of cancer remains high, then a pleural biopsy is recommended.

Before considering a lung resection or a treatment by radiation therapy, pulmonary function tests should be obtained, including spirometry and a measure of the lung diffusion capacity. The forced expiratory volume in the first second FEV1 and the lung diffusion capacity should be calculated based on projected postoperative predicted values, according to the percentage of lung that is to be resected. If the predicted postoperative FEV1 and lung diffusion capacity are greater than 60%, then no further pulmonary function testing is required. If not, then a qualitative lung perfusion scan and/or a cardiorespiratory exercise test should be obtained.¹⁰

Treatment of Non-Small Cell Carcinomas

Stages I and II

Surgical treatment remains the first choice. A procedure with thoracoscopy is preferable for stage I cancers. The lobectomy remains the standard choice with respect to less invasive surgery. Among less invasive surgeries, a segmentectomy is a preferred option with respect to a wedge resection. These options are considered if the pulmonary function tests are prohibitively low or in the presence of significant comorbid conditions. A pneumonectomy is performed only if, from an oncological perspective, a smaller sleeve resection is not possible. For stage II lung cancer with lymph node invasion in a patient with a good performance status, adjuvant platinum-based chemotherapy is recommended over four cycles. Similar recommendations are offered for stage IIIA (N2 node) that is diagnosed postoperatively when the resected tissue is analyzed. Adjuvant radiotherapy is recommended only if the resection is incomplete.

If the patient cannot tolerate surgery, then stereotactic body radiation therapy (SBRT) is recommended for tumours less than 5 cm in patients with stage I cancer without suspicious lymph nodes.¹¹ This therapy consists of high-dose radiation therapy provided in several fractions. The therapy is of a shorter duration (3–5 days) than conventional radiation therapy (30 days). Current studies suggest that local control is excellent with a 90% success rate three years after the procedure. No phase III clinical trials compare surgical therapy to this new radiation therapy, since most of these studies failed due to lack of recruitment. It will be difficult to obtain a clear comparison between these two therapeutic modalities, particularly since the pathological staging is not done in patients undergoing SBRT, and several patients are not willing to be subjected to the short-term morbidity and mortality associated with surgical therapy. The current indication of SBRT is therefore mainly in patients who have poor lung function tests and other significant comorbid conditions that preclude a surgical resection. If SBRT is not possible, then conventional radiation therapy is recommended, but the results are clearly inferior to surgical resection or SBRT.

Stage III

The treatment of stage III non-small cell lung carcinomas is more controversial. For most of these patients, a combination of chemotherapy using a platinum-based medication and radiation therapy is recommended if the performance status is good (ECOG 0 or 1) and if there is no significant weight loss during treatment (less than 5–10% weight loss over the last few months). The dose of radiation therapy is approximately

60 Gy. Concomitant chemotherapy and radiation therapy are superior to sequential therapies (chemotherapy followed by radiation therapy). If the patient is too ill, then palliative radiation therapy alone is recommended.

Certain patients will require a neoadjuvant treatment (chemotherapy combined with or without radiation therapy) if the mediastinal disease is limited to a single lymph node in the ipsilateral para-tracheal (N2) region, and this therapy is followed by surgical resection. This approach is controversial, as it has not been demonstrated to be superior to concomitant chemotherapy and radiation therapy.

For patients with stages I or II disease who have undergone lung resection and in whom the postoperative analyses reveal that it is a stage IIIA (N2 lymph node involvement) disease, adjuvant chemotherapy is recommended. Adjuvant radiation therapy is only recommended in patients in whom the lung resection is incomplete. For certain selected cases, if the risk of local recurrence is high, then adjuvant radiation therapy after adjuvant chemotherapy can be considered to decrease the risk of local recurrence.

Stage IV

Palliative chemotherapy is recommended in patients with a good performance status (0, 1, or even 2). The first line of therapy depends on the histology and on the results of molecular test for adenocarcinomas. A total of three lines of chemotherapy have been shown to be beneficial for the survival of patients and their quality of life.

For the first line of chemotherapy, survival benefits are approximately 3–4 months when a combination of platinum-based agents (cisplatin or carboplatin) are used with a second agent, such as gemcitabine, paclitaxel, or pemetrexed. Carboplatin is associated with fewer adverse events, such as renal insufficiency, neuropathy, nausea, and vomiting. This treatment is provided over four cycles and sometimes up to six cycles.

If the lung cancer is not a squamous cell type, then pemetrexed can be used, since it is more effective. Pemetrexed is associated with clinical deterioration in patients with squamous cell carcinomas. This agent is contraindicated in patients with squamous cell carcinomas, as is bevacizumab (a monoclonal antibody against vascular endothelial growth factor that is given in combination with chemotherapy). Bevacizumab is rarely prescribed for patients with lung cancer because of its poor cost/benefit ratio.

If the tumour is an adenocarcinoma with an EGFR positive mutation (particularly exons 19 and 21), then a tyrosine kinase inhibitor (gefitinib, erlotinib, afatinib) will be prescribed

because of the superior efficacy quality-of-life and adverse effects profile. These tumours also generally have a better prognosis. Such tumours are more common in patients who have not smoked cigarettes and who are of Asian origin. If the tumour is an adenocarcinoma with an ALK rearrangement, then an ALK tyrosine kinase inhibitor (crizotinib) will provide superior efficacy and a better quality of life. This is a major change in clinical practice based on targeted therapy. This treatment is an oral medication in contrast to conventional chemotherapy, which is usually intravenous. Furthermore, there is no febrile neutropenia associated with these agents. In the coming years, it is likely that many other targeted therapies will be available for adenocarcinomas, and similar studies are being initiated for squamous cell carcinomas.¹²

Chemotherapy maintenance therapy is possible if there is no evidence of progression after the first line of therapy in patients with a good performance status (0, 1). This therapy is continued as long as there is no evidence of progression and the adverse effects are well tolerated. Survival benefits are observed over 1–5 months, according to the histological type and the chemotherapy agent used (pemetrexed, erlotinib).

The second line of therapy includes docetaxel or pemetrexed (if not previously prescribed). These agents provide approximately two months of survival benefit. Erlotinib is also used as a second-line therapy, particularly for patients who are not good candidates for the other second-line therapies. In the third-line therapy, only erlotinib has proven to have some survival benefits.

Prognosis

Five-year survival depends mainly on the stage of the lung carcinoma (Table 3). The general five-year survival rate is approximately 17%.

Table 3. Prognosis of Non-Small Cell Carcinomas

Stage	5-year survival
IA	73%
IB	58%
IIA	46%
IIB	35%
IIIA	19–24%
IIIB	7–9%
IV	2%

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Small Cell Carcinoma Therapy

For stages I to III small cell carcinomas (previous limited stage), chemotherapy based on cisplatin-etoposide associated with radiation therapy is recommended in concomitant therapy. Four cycles of chemotherapy are given. Radiation therapy can be provided according to various protocols, with a total radiation of 40–60 Gray (Gy). A sequential treatment of chemotherapy followed by radiation therapy is prescribed if there are contraindications to concomitant therapy. Very rarely is small cell carcinoma removed surgically, and this is only done if the tumour is of a small size and there is no evidence of lymph node involvement or metastatic disease. Stage IV small cell carcinomas require chemotherapy with a regimen based on platinum and etoposide over four to six cycles.

Cerebral prophylaxis with the radiation therapy is prescribed if there is a complete therapeutic response in the limited stages. At the 2014 American Society of Clinical Oncology Conference (ASCO), evidence was provided demonstrating there is no survival advantage for extensive stages in which cerebral prophylaxis is added, based on the initial imaging of the brain with magnetic resonance.¹³

If recurrence occurs, then a therapy using topotecan or a combination of cyclophosphamide, doxorubicine, vincristine (CAV) can be offered. The response rate is generally poor. If recurrence occurs more than six months after the end of the treatment, then a platinum-etoposide treatment is usually prescribed once again.

Follow-Up

No standard follow-up has been demonstrated as being beneficial for patient survival. In general, patients will be followed up every 3–6 months for the first 2 years and every 6–12 months for the next 3–5 years. Annual follow-ups will be done afterwards. Routine imaging involves chest X-ray or CT scan. Chest CT scans are usually not obtained more than once a year.

Future Trends

The coming years will see a more extensive use of endoscopic ultrasound, stereotactic body radiation therapy, and molecular therapy. At ASCO conference 2015, exciting results from trials on immunotherapy have been presented, especially regarding nivolumab in second line therapy for advanced squamous cell carcinoma.

Conflict of Interest

The senior author has made several presentations on lung cancer (new TNM classification, endobronchial ultrasound, new therapies for metastatic stages, lung cancer screening) and received honoraria from the pharmaceutical industry for some of these presentations.

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A Systematic Review of Combination Therapies for Smoking Cessation

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Abstract

Introduction: The use of pharmacological and behavioural therapies has been shown to help smokers quit. However, the efficacy of combining smoking cessation therapies remains poorly understood. We conducted a systematic review of randomized controlled trials (RCTs) with factorial designs to assess the efficacy of combination smoking cessation therapies.

Methods: We performed a systematic search of the Cochrane Library, EMBASE, PsycINFO, and PubMed databases for RCTs of combination therapies for smoking cessation. We included RCTs with factorial designs, reporting biochemically validated point prevalence or continuous abstinence outcomes at 6 or 12 months. Combination therapies were either two pharmacotherapies or a pharmacotherapy with behavioural therapy. Pharmacotherapies included nicotine replacement therapies (NRTs), bupropion, and varenicline. Behavioural therapies included counselling and minimal intervention.

Results: A total of 11 RCTs met our inclusion criteria: 4 combinations of pharmacotherapies and 7 combinations of a pharmacotherapy with behavioural intervention. Combinations were two NRTs (2 RCTs), bupropion with NRT (3 RCTs), bupropion with behavioural intervention (4 RCTs), and NRT with behavioural intervention (3 RCTs). No identified trials combined varenicline with other included pharmacotherapies. Combining pharmacotherapies did not increase smoking abstinence at 6 or 12 months, compared with pharmacological monotherapies. Evidence suggests a modest yet inconsistent benefit from combining pharmacotherapy with behavioural therapy.

Conclusion: Evidence from RCTs with factorial designs does not conclusively show combination smoking cessation therapies to be superior to monotherapies. Pharmacotherapies could be prescribed without behavioural therapy, with minimal loss of treatment efficacy.

Key words: Smoking cessation, combination therapy, systematic review

Résumé

Introduction : La pharmacothérapie et la thérapie comportementale sont efficaces dans la désaccoutumance au tabac. Cependant, l'efficacité d'interventions combinées reste à déterminer. Nous avons procédé à l'étude systématique d'essais cliniques comparatifs et randomisés (ECR) au plan factoriel pour évaluer l'efficacité de thérapies combinées dans la désaccoutumance au tabac.

Méthode : Nous avons effectué une recherche documentaire systématique dans les bases de données The Cochrane Library, EMBASE, PsycINFO et PubMed en quête d'ECR sur des interventions combinées dans le renoncement au tabac. Nous avons retenu des ECR au plan factoriel faisant état de la prévalence ponctuelle validée de manière biochimique ou de l'abstinence continue en 6 ou 12 mois. La thérapie combinée peut englober deux pharmacothérapies ou la thérapie comportementale et la pharmacothérapie. La pharmacothérapie consiste en une thérapie de remplacement de la nicotine (TRN) ou en l'emploi de bupropion ou de varénicline. La thérapie comportementale comprend le counseling et une intervention de courte durée.

Résultats : Nous avons relevé 11 ECR qui satisfont les critères d'inclusion : 4 sur une combinaison de pharmacothérapies et 7 sur l'association d'une pharmacothérapie et d'une intervention comportementale. Les interventions combinées étudiées sont deux TRN (2 ECR), le bupropion combiné à une TRN (3 ECR), le bupropion combiné avec une intervention comportementale (4 ECR) et une TRN associée à une intervention comportementale (3 ECR). Aucun des ECR n'évalue la varénicline combinée avec une autre pharmacothérapie. La combinaison de pharmacothérapies n'augmente pas l'abstinence du tabac en 6 ou 12 mois comparativement à une pharmacothérapie seule. Les données probantes laissent entrevoir un avantage modeste, quoiqu'inconstant, à l'association d'une pharmacothérapie et de la thérapie comportementale.

Conclusion : Les données probantes provenant d'ECR au plan factoriel ne sont pas concluantes quant à la supériorité des thérapies combinées sur la monothérapie dans la désaccoutumance au tabac. La pharmacothérapie pourrait être prescrite seule, sans la thérapie comportementale, et l'on ne perdrait pas grand-chose en efficacité.

Introduction

Smoking cessation without the aid of adjunctive pharmacological or behavioural therapy remains challenging, with only 3–5% of people remaining abstinent beyond 6–12 months.¹ While use of pharmacological monotherapies has been shown to roughly double quit rates, compared to placebo,² the probability of successfully quitting with pharmacological monotherapies remains low. Due to differences in their mechanisms of action, combining smoking cessation pharmacotherapies may confer a greater therapeutic benefit relative to pharmacological monotherapies. Behavioural therapy, which is modestly effective when used alone,³ has also been recommended as an adjunct to pharmacotherapy.⁴ It remains unclear whether the combination of smoking cessation therapies provides additional benefits beyond those of individual therapies administered alone. Therefore, the objective of this systematic review was to examine the efficacy of combination smoking cessation therapies, including combined pharmacotherapies and pharmacotherapy combined with behavioural therapy.

Methods

Search Strategy

Our systematic review was performed with a pre-specified protocol and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁵ We searched the Cochrane Library, PubMed, EMBASE, and PsycINFO databases from inception to April 2013, using medical subject heading (MeSH) terms, Emtree terms, and key words for smoking cessation, pharmacotherapies, and behavioural therapies. Our search, designed by a medical liaison librarian (GG), and reported in detail in online Appendices 1–4,[†] was limited to articles published in English or French. Database-specific hedges were used to limit the search to RCTs not conducted in animals.⁶

Study Selection

We included RCTs with factorial designs of combined smoking cessation therapies that reported biochemically validated (e.g., using cotinine or exhaled carbon monoxide) prevalence of smoking abstinence at 6 and/or 12 months

(± 4 weeks). Inclusion was restricted to RCTs with factorial designs; such RCTs are ideal for studying combination smoking cessation therapies due to the possibility of exploring interactions between two or more treatments for a given dependent variable (e.g., smoking abstinence). Interventions included pharmacotherapies combined with each other and a pharmacotherapy combined with behavioural therapy.

Pharmacotherapies included nicotine replacement therapy (NRT), bupropion, and varenicline. Behavioural therapies included counselling or minimal clinical intervention; alternative treatments such as hypnosis or acupuncture were not considered in this review. RCTs where the intervention and control groups received adjunctive support were included if the adjunctive support was permitted equally in all groups. Trials in which sub-therapeutic dosages of pharmacotherapies were used as the placebo group were permitted. We excluded letters to the editor, editorials, reviews, and abstracts from conference proceedings, trials in non-cigarette tobacco users, as well as trials in which participants were not motivated to quit.

Data Extraction

Two reviewers independently extracted data, with disagreements resolved by consensus or a third party. Extracted data included demographic and clinical characteristics,

treatment and dosage regimens, adverse events, and biochemically validated smoking cessation outcomes. Smoking abstinence was reported either as point prevalence and/or continuous abstinence. Point prevalence abstinence was defined as self-reported, biochemically validated abstinence in the seven days preceding the follow-up visit. Continuous abstinence was defined as self-reported abstinence throughout the follow-up period, with biochemical validation at all follow-up visits. Participants who were lost to follow-up or withdrew were classified as having returned to smoking.

Quality Assessment

Quality assessment was performed with Cochrane Collaboration's tool for assessing risk of bias.⁷ This tool allows for the categorization of RCTs based on the likelihood of potential threats to validity from selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Risk of bias was classified as low, unclear, or high. Two reviewers independently performed quality assessment, with disagreements resolved by consensus or a third reviewer.

Results

The electronic search generated 12,232 potentially relevant publications, of which 355 full-text records were reviewed (Figure 1). Of these, 12 records met our eligibility criteria,

RCTs = randomized controlled trials.

Figure 1. PRISMA flowchart outlining systematic literature search and study selection.

including four trials^{8–11} of combination pharmacotherapies (online Appendix 5),[†] and eight trials^{12–19} of combination pharmacotherapy with behavioural therapy (online Appendix 6).[†] We were unable to examine the efficacy of combining varenicline with other smoking cessation therapies, as no varenicline trials met our inclusion criteria.

Characteristics of Included RCTs

Included trials randomized a total of 6,264 participants. Overall, point prevalence abstinence at 6 months was reported in 10 RCTs^{8–10,12–18} and at 12 months in 10 RCTs.^{8,10–11,13–19} Continuous abstinence was reported in five RCTs (online Appendix 7),[†] all of which reported 12-month abstinence data, and four^{10,11,17,18} of which reported six-month abstinence data. Studies by Tonnesen and colleagues¹¹ and Swanson and others¹⁰ were conducted open-label and thus had a high risk of bias due to lack of blinding (online Appendix 8).[†] Several studies^{13–16,18,19} inadequately described the process by which participants were allocated to treatment groups. However, the included studies had a low risk of bias in all other domains.

Characteristics of Participants Within Included RCTs

The majority of included trials were conducted in adult smokers from the US (Table 1), with the exception of participants in trials by Swanson et al.¹⁰ (conducted in smokers in the US Navy), Ahluwalia et al.¹² (conducted in African American adults), Tonnesen et al.¹⁴ (conducted in smokers with chronic obstructive pulmonary disease), and Levine et al.¹⁸ (conducted in female smokers). Most participants were middle-aged Caucasian smokers recruited from the general population. On average, participants were smoking a pack per day at baseline and had previously made at least three attempts to quit smoking.

Combined Pharmacotherapies

Two RCTs were identified that included NRT combinations. The first¹¹ ($n = 446$) used a two-by-two factorial design to examine the efficacy of nicotine patch and nicotine inhaler (Table 2). Overall, 12-month point prevalence abstinence was low in all groups: combination NRT (11%), patch alone (16%), inhaler alone (9%), and placebo (6%). Only participants randomized to the nicotine patch alone had significantly higher point prevalence abstinence at 12 months, compared to placebo (odds ratio [OR] 2.85; 95% confidence interval [CI] 1.13–7.18). In the second, Piper et al.⁹ ($n = 1,504$) randomized patients to one of six treatment arms: 1) nicotine patch and nicotine lozenge combination therapy; 2) nicotine lozenge and bupropion combination therapy; 3) nicotine patch

Table 1. Characteristics of Participants within Included Trials.

Type	Study (Year)	Country	Population	Age* (Years)	Men* (%)	Caucasian* (%)	Daily Cigarettes Smoked*	Years Smoked*	Quit Attempts Made*	FTND*	FTQ*
Pharmacotherapy Combination†	Piper (2009)	US	Adult smokers	44.7	41.8†	83.9	21.4	–	5.7	5.4	–
	Jorenby (1999)	US	Adult smokers	43.3†	47.7†	93.0†	26.6†	26.0†	2.8†	–	7.4
	Tonnesen (2000)	Denmark	Adult smokers	49.2†	46.2†	–	18.6†	–	–	1.6	–
	Swanson (2003)	US	Navy smokers	27.1	94.0	80.0	19.0	9.4†	3.1†	5.6	–
Behavioural with NRT	Ahluwalia (2006)	US	African American	45.1†	33.1†	0.0	7.5†	23.9†	3.2†	4.3†	–
	Killen (1997)	US	Adult smokers	45.4	50.3†	82.0†	23.5†	–	–	–	16.8
	Tonnesen (2006)	US	Smokers with COPD	61.0	47.8†	–	19.6	–	2.6†	6.2	–
	Hall (1987)	US	Adult smokers	39.0	53.0	94.0	30.0	–	–	–	–
Behavioural with Bupropion	Brown (2007)	US	Adult smokers	44.3	52.5†	92.0	24.6	26.0	–	6.41	–
	McCarthy (2008)	US	Adult smokers	38.8	49.7†	89.0†	21.9†	–	6.0†	5.1	–
	Levine (2010)	US	Female smokers	42.0	0.0	86.0	20.7	–	3.1	5.2	–
	Hall (2002)	US	Adult smokers	39.4	56.2†	78.8†	21.9†	21.7†	6.2†	4.8	–

COPD = chronic obstructive pulmonary disease, FTQ = Fagerstrom Tolerance Questionnaire, FTND = Fagerstrom Test of Nicotine Dependence, NRT = nicotine replacement therapy, US = United States.

*Numbers reported as means of all participants unless otherwise stated.

†Combination pharmacotherapies include NRTs with or without bupropion.

‡Calculated from data presented in original paper.

Table 2. Smoking Abstinence in Combination Pharmacotherapy Trials.

Trial	Pharmacological Therapy	n	Duration of Treatment	6 months				12 months			
				PP		Loss to Follow-Up (%)†	PP Abstinence (%)	PP		Loss to Follow-Up (%)†	Odds Ratio (CI)*
				Abstinence (%)	Odds Ratio (CI)*			Abstinence (%)	Odds Ratio (CI)*		
Piper (2009)	Bupropion / Nicotine lozenge	262	Nicotine patch	33.2‡	1.74 (1.13–2.67)	4.6	–	–	–	–	–
	Nicotine patch / Nicotine lozenge	267	x 12 weeks	40.1‡	2.34 (1.54–3.57)	3.4	–	–	–	–	–
	Bupropion	264	Bupropion	31.8‡	1.63 (1.06–2.51)	7.6	–	–	–	–	–
	Nicotine lozenge	260	x 9 weeks	33.5‡	1.76 (1.15–2.70)	8.5	–	–	–	–	–
	Nicotine patch	262	Nicotine lozenge	34.4‡	1.83 (1.20–2.81)	4.6	–	–	–	–	–
Jorenby (1999)	Placebo / Placebo§	189	x 12 weeks	22.2‡	1.00 (ref.)	6.0	–	–	–	–	–
	Nicotine patch / Bupropion	245	Nicotine patch	38.8	2.7 (1.7–4.4)	20.4	–	35.5	3.0 (1.8–4.9)	26.1	–
	Placebo patch / Bupropion	244	x 8 weeks	34.8	2.3 (1.4–3.7)	27.0	–	30.3	2.3 (1.4–3.9)	30.7	–
	Nicotine patch / Placebo pill	244	Bupropion	21.3	1.2 (0.7–1.9)	34.8	–	16.4	1.1 (0.6–1.8)	37.8	–
	Placebo patch / Placebo pill	160	x 9 weeks	18.8	1.00 (ref.)	46.3	–	15.6	1.00 (ref.)	48.8	–
Tonnesen (2000)	Nicotine patch / Nicotine inhaler	115	All treatments	–	–	–	–	11.0‡	1.86 (0.71–4.85)	88.8	–
	Nicotine inhaler	118	x 12 weeks	–	–	–	–	9.0‡	1.50 (0.56–4.01)	–	–
	Nicotine patch	104	–	–	–	–	–	16.0‡	2.85 (1.13–7.18)	–	–
	Placebo patch / Placebo inhaler	109	–	–	–	–	–	6.0‡	1.00 (ref.)	–	–
Swanson (2003)	Nicotine patch / Bupropion	29	All treatments	13.8‡	0.98 (0.26–3.69)	–	–	17.2‡	0.95 (0.28–3.16)	27.6	–
	Bupropion	21	x 9 weeks	4.8‡	0.26 (0.03–2.24)	–	–	19.0‡	1.07 (0.29–3.96)	33.3	–
	Nicotine patch	31	–	19.4‡	1.26 (0.39–4.05)	–	–	12.9‡	0.67 (0.19–2.41)	22.6	–
	No treatment	50	–	16.0‡	1.00 (ref.)	–	–	18.0‡	1.00 (ref.)	36.0	–

CI = confidence interval, PP = point prevalence, ref = reference group.

*Odds ratio (confidence interval) with placebo or no treatment serving as the reference group.

† Loss to follow-up calculated as the difference between the number of participants randomized to each group and the number of participants successfully followed-up.

‡ All trials treated participants lost to follow-up as having returned to smoking.

#Number of abstinent participants calculated from percentage abstinent multiplied by the number of participants randomized to each group.

§ Five distinct placebo conditions matched each of the active treatment conditions: placebo bupropion, placebo lozenge, placebo patch, placebo patch plus lozenge, and placebo bupropion plus lozenge.

||Percent of abstinent participants calculated from the number of abstinent participants divided by the number of participants randomized to each group, multiplied by 100%.

Table 3. Smoking Abstinence in Nicotine Replacement Therapy and Behavioural Therapy Combination Trials.

Trial	Pharmacological/ Behavioural Therapy	n	Duration of Treatment	6 months				12 months			
				PP Abstinence (%)	Odds Ratio (CI)*	Loss to Follow-Up (%)†	PP Abstinence (%)	Odds Ratio (CI)*	Loss to Follow-Up (%)†	PP Abstinence (%)	Loss to Follow-Up (%)†
Ahluwalia (2006)	Nicotine gum / Motivational interview	189	Nicotine gum x 8 weeks	15.3	0.58 (0.34–0.97)	—	—	—	—	—	—
	Nicotine gum / Health education	189	weeks	29.1	1.30 (0.82–2.06)	118 (15.6%)	—	—	—	—	—
	Placebo gum/ Motivational interview	189	Counselling	14.8	0.55 (0.33–0.93)	—	—	—	—	—	—
	Placebo gum/ Health education	188	x 16 weeks	23.9	1.00 (ref.)	—	—	—	—	—	—
Killen (1997)	Nicotine patch / Manual & video	109	All treatments x 16 weeks	14.7	0.82 (0.39–1.71)	—	12.8	0.95 (0.43–2.10)	12.8	—	—
	Nicotine patch / Manual	103	16 weeks	24.3	1.53 (0.78–3.02)	—	19.4	1.55 (0.74–3.26)	16.5	—	—
	Placebo patch/ Manual & video	108	—	11.1	0.60 (0.27–1.31)	—	9.3	0.66 (0.28–1.55)	13.0	—	—
	Placebo patch/ Manual	104	—	17.3	1.00 (ref.)	—	13.5	1.00 (ref.)	13.5	—	—
Tonnesen (2006)	Nicotine pill / High support	115	Nicotine pill x 12 weeks, ≤12 months	24.0	5.37 (1.93–14.93)	—	18.0	3.59 (1.25–10.28)	22.2	—	—
	Nicotine pill / Low support	118	—	22.0	4.71 (1.69–13.12)	—	17.0	—	—	—	—
	Placebo pill/ High support	104	months	13.0	2.57 (0.88–7.53)	—	13.0	3.36 (1.18–9.61)	—	—	—
	Placebo pill/ Low support	109	Counselling x 12 months	6.0	1.00 (ref.)	—	6.0	2.57 (0.88–7.53)	—	—	—
Hall (1987)	Nicotine gum / Intensive	29	Counselling x 12 months	43.0	1.38 (0.52–3.63)	—	34.0	2.01 (0.68–5.96)	5.7	—	—
	Nicotine gum / Low contact	21	months	56.0	2.29 (0.88–6.00)	—	50.0	3.86 (1.34–11.10)	5.6	—	—
	Placebo gum / Intensive	31	—	21.0	0.48 (0.16–1.41)	—	21.0	1.00 (0.31–3.24)	11.8	—	—
	Placebo gum / Low contact	50	—	35.0	1.00 (ref.)	—	21.0	1.00 (ref.)	8.8	—	—

CI = confidence interval, PP = point prevalence.

*Odds ratio (confidence interval) with placebo or no treatment serving as the reference group.

†Loss to follow-up was calculated as the difference between the number of participants randomized to each group and the number of participants successfully followed-up. All trials treated participants lost to follow-up as having returned to smoking.

Table 4. Smoking Abstinence Outcomes in Combination Bupropion and Behavioural Therapy Trials.

Trial	Pharmacological/ Behavioural Therapy	n	Duration of Treatment	6 months			12 months		
				PP Abstinence (%)	Odds Ratio (CI)*	Loss to Follow-Up (%)†	PP Abstinence (%)	Odds Ratio (CI)*	Loss to Follow-Up (%)†
Brown* (2007)	Bupropion / CBTD	108		23.2	1.39 (0.76–2.54)	–	17.6	1.18 (0.61–2.29)	–
	Bupropion / CBT	147	All treatments	27.9	1.78 (1.03–3.07)	–	22.5	1.60 (0.90–2.87)	–
	Placebo pill/ CBTD	112	x 12 weeks	15.2	0.82 (0.43–1.59)	–	17.9	1.21 (0.63–2.31)	–
	Placebo pill / CBT	157		17.8	1.00 (ref.)	–	15.3	1.00 (ref.)	–
McCarthy (2008)	Bupropion / Standard counselling	157	Bupropion	18.6	1.61 (0.78–3.36)	38.1	21.1	1.52 (0.77–3.02)	38.1
	Bupropion	113	x 9 weeks	13.8	1.13 (0.52–2.44)	44.0	20.7	1.47 (0.74–2.92)	32.8
	Placebo pill / Standard counselling	116	Counselling	12.4	1.00 (0.46–2.18)	52.1	12.4	0.80 (0.38–1.69)	38.8
	Placebo pill	121	x 4 weeks	12.4	1.00 (ref.)	46.9	15.0	1.00 (ref.)	38.1
Levine* (2010)	Bupropion / Weight concerns‡	113	Bupropion	37.0	3.75 (1.68–8.40)	40.0	29.0	2.10 (0.97–4.55)	46.2
	Bupropion / Standard counselling	106	x 26 weeks	26.0	2.25 (0.96–5.24)	47.2	27.0	1.88 (0.85–4.18)	48.3
	Placebo pill / Weight concerns‡	89	Counselling	11.0	0.84 (0.32–2.19)	54.0	10.0	0.59 (0.23–1.51)	57.5
	Placebo pill / Standard counselling	87	x 12 weeks	13.0	1.00 (ref.)	52.2	16.0	1.00 (ref.)	58.2
Hall* (2002)	Bupropion / Psychological	67	Bupropion	–	4.20 (1.05–16.78)	10.8	–	2.65 (0.74–9.55)	16.2
	Bupropion / Medical management	37	x 12 weeks	–	3.24 (0.78–13.37)	13.9	–	2.75 (0.76–9.92)	13.9
	Placebo pill / Psychological	36	Counselling	–	3.78 (0.93–15.33)	19.4	–	1.65 (0.42–6.41)	22.2
	Placebo pill / Medical management	36	x 11 weeks	–	1.00 (ref.)	16.2	–	1.00 (ref.)	16.2

Abbreviations: CBT = cognitive behavioural therapy for smoking cessation, CBTD = cognitive behavioural therapy for smoking cessation and depression.

*Odds ratios calculated based on published abstinence data.

† Loss to follow-up data were calculated as the difference between the number of participants randomized to each group and the number of participants followed-up. All trials treated participants lost to follow-up as having returned to smoking.

‡ "Weight concerns" involved counselling regarding weight management strategies to avoid weight gain occurring during smoking cessation.

Table 5. Adverse Events for Each Treatment Group of Combination Pharmacotherapy Trials.

	Jorenby et al. (1999)						Piper et al. (2009)					
	Treatment Groups						Treatment Groups					
	Placebo patch Placebo pill	Nicotine patch Placebo pill	Placebo patch Bupropion	Nicotine patch Bupropion	Placebo Bupropion	Nicotine patch Bupropion	Nicotine patch lozenge	Bupropion lozenge	Nicotine patch lozenge	Bupropion lozenge	Nicotine patch lozenge	Bupropion lozenge
n	160	244	244	245	189	262	260	264	267	262	74	77
Adherence (%)	51.2	64.3	68.9	71.4	75	86	67	85	74	77		
Adverse Events (%)												
Dry mouth	4.4	4.1	10.7	9.0	1.0	0.2	0.0	3.8	0.2	3.8		
Nausea	5.0	7.8	9.5	11.5	4.4	4.3	7.8	3.8	7.9	5.0		
Vomiting	–	–	–	–	1.1	1.0	1.4	1.9	1.6	1.4		
Diarrhea	–	–	–	–	1.1	1.4	2.3	1.5	1.0	1.7		
Dyspepsia	–	–	–	–	1.1	1.0	0.2	1.0	3.6	3.5		
Application-site reaction	6.9	18.5	11.9	15.2	–	–	–	–	–	–		
Itching	–	–	–	–	2.7	14.7	1.0	2.7	8.9	2.1		
Dermatological	0.0	0.0	2.0	1.0	–	–	–	–	–	–		
Dizziness	6.3	3.3	10.7	8.2	1.7	1.2	1.0	1.1	1.3	2.3		
Insomnia	19.5	30.0	42.4	47.5	–	–	–	–	–	–		
Dream abnormalities	2.5	18.1	4.5	13.5	5.6	11.3	3.2	16.8	9.0	10.6		
Infection	15.7	14.8	14.8	15.2	–	–	–	–	–	–		
Headache	32.7	28.4	25.9	26.6	6.7	4.4	5.1	4.4	4.9	4.6		
Rhinitis	12.0	12.4	13.6	10.7	–	–	–	–	–	–		
Influenza-like syndrome	10.7	7.4	8.6	7.8	–	–	–	–	–	–		
Serious AE			5					32				
Drug DC due to AE (%)	6	16	29	28	1	0	0	2	0	1		
Total events (n)	–	–	–	–	359	585	566	524	697	654		

AE = adverse event, DC = discontinuation.

Total events were reported as the number of events in each group, whereas each specific adverse event type reported as percent of participants who experienced a particular event.

monotherapy; 4) nicotine lozenge monotherapy; 5) bupropion monotherapy; and 6) placebo. Participants in the combination NRT arm had a higher point prevalence of abstinence (40.1%) at six months, relative to all other trial arms. However, while all treatment arms led to significantly increased abstinence outcomes relative to placebo, no significant difference was found between active treatment groups.

The two additional pharmacotherapy trials examined nicotine patch combined with bupropion (Table 2). Jorenby et al.⁸ ($n = 893$) reported greater 12-month point prevalence of abstinence among participants randomized to the nicotine patch combined with bupropion (35.5%), followed by placebo patch with bupropion (30.3%), nicotine patch with placebo pill (16.4%), and placebo patch with placebo pill (double placebo, 15.6%). Nicotine patch combined with bupropion (OR 3.0, 95% CI 1.8–4.9) was significantly better than double placebo, but there was no evidence to suggest it was superior to the nicotine patch with placebo pill (OR 1.1, 95% CI 0.6–1.8). Abstinence in the bupropion and placebo patch arm was also significantly higher than in the double placebo arm (OR 2.3, 95% CI 1.4–3.7). No difference was found between the other treatment arms. Swanson et al.¹⁰ ($n = 131$) found no differences in 12-month abstinence among participants randomized to nicotine patch combined with bupropion (OR 0.95, 95% CI 0.28–3.16), nicotine patch monotherapy (OR 0.67, 95% CI 0.19–2.41), bupropion monotherapy (OR 1.07, 95% CI 0.29–3.96), or placebo (reference group).

NRT Combined with Behavioural Therapy

Four two-by-two factorial design RCTs combined NRT or placebo with high support or low support behavioural interventions (Table 3). Ahluwalia et al.¹² ($n = 755$) paired nicotine gum with motivational interviewing or health education. Killen et al.¹³ ($n = 424$) combined nicotine patch with one of two self-help behavioural interventions: a video-enhanced self-help treatment manual or a self-help treatment manual only. Both Tonnesen et al.¹⁴ ($n = 370$) and Hall et al.¹⁵ combined high- or low-intensity smoking cessation counselling with a nicotine tablet or nicotine gum, respectively.

No trial showed a significant benefit from high-intensity behavioural interventions, compared to low-intensity behavioural interventions in groups receiving NRT. There was also no significant benefit observed for high support versus low support in groups receiving placebo. In the trial conducted by Tonnesen et al.,¹⁴ both groups receiving NRT (irrespective of the intensity of counselling) were significantly more likely to be abstinent at 12 months than the group that received placebo and low support (high support OR 3.59, 95%

CI 1.25–10.28; low support OR 3.36, 95% CI 1.18–9.61). In the trial conducted by Ahluwalia et al.,¹² six-month point prevalence of abstinence showed a negative treatment effect for both groups receiving motivational interviewing, compared with the placebo and health education group (nicotine gum OR 0.58, 95% CI 0.34–0.97; placebo gum OR 0.55, 95% CI 0.33–0.93). The authors theorized that this effect was due to differential attrition between motivational interview and health education groups ($p = 0.004$). Neither Killen et al.¹³ nor Hall et al.¹⁵ found significant differences in point prevalence abstinence at either 6 or 12 months across all treatment arms. An exception to this finding applied to participants in the trial by Hall and colleagues randomized to nicotine gum and low-intensity behavioural counselling, compared to placebo gum with low-intensity behavioural counselling (12-month OR 3.59, 95% CI 1.34–11.10).

Bupropion Combined With Behavioural Therapy

Four two-by-two factorial design trials combined bupropion or placebo with behavioural interventions (Table 4). Brown et al.¹⁶ ($n = 524$) paired bupropion with cognitive behavioural therapy for smoking cessation (CBT) or cognitive behavioural therapy for smoking cessation and depression (CBTD). McCarthy et al.¹⁷ ($n = 463$) combined bupropion with a standard form of smoking cessation counselling. Levine et al.¹⁸ ($n = 349$) combined bupropion with CBT for smoking-related weight concerns or with standard counselling. Hall et al.¹⁹ ($n = 146$) combined bupropion with a medical management intervention consisting of cessation advice, antidepressant administration, adverse effects monitoring and educational materials, or medical management with a psychological intervention consisting of health-related information for mood management and smoking cessation.

Across all trials, no significant difference was found between treatment groups relative to their respective reference groups at 12 months. At six months, Brown et al.¹⁶ found that participants randomized to bupropion with CBT had a significantly greater point prevalence of abstinence relative to placebo with CBT (27.9% versus 17.8%; OR 1.78, 95% CI 1.03–3.07). Levine et al.¹⁸ found that patients randomized to bupropion and weight-concern counselling had significantly greater six-month point prevalence of abstinence, compared to those randomized to placebo with standard counselling (37.0% versus 13.0%; OR 3.75, 95% CI 1.68–8.40). Similarly, Hall et al.¹⁹ found bupropion combined with psychological counselling resulted in favourable outcomes relative to placebo with medical management at six months (OR 4.20, 95% CI 1.05–17.78). However, for all trials, these differences were no longer significant at 12 months.

Tolerability of Combination Therapies

Among the four trials^{14,17–19} that reported overall adverse event data, no serious adverse events occurred significantly more frequently among combination therapy groups, compared to monotherapy groups. Adverse event data stratified by treatment arm were available from Jorenby et al.⁸ and Piper et al.⁹ (Table 5). While Jorenby et al. did not comment on the significance of differences between adverse events in combination pharmacotherapy versus pharmacological monotherapy, Piper et al. concluded that combination therapy did not result in a clinically significant increase in adverse events, compared to pharmacological monotherapy.

In the trial by Jorenby et al.,⁸ the combined nicotine patch and bupropion group had the highest adherence (71.4%) of any group. Drug discontinuation due to adverse events was higher in both bupropion groups (bupropion with patch, 28%; bupropion with placebo patch, 29%) compared to patch and placebo pill (16%) and placebo patch and placebo pill (6%). Adverse events that occurred more frequently in the combination group included nausea (11.5%) and insomnia (47.5%). In the study by Piper et al.,⁹ the addition of nicotine lozenge to patch (74%) and to bupropion (77%) appeared to reduce adherence, compared to patch (86%) and bupropion (85%) alone; however, there were very few drug discontinuations due to side effects in any group. Dyspepsia was the only adverse event, which occurred more frequently in the combination groups, compared to monotherapy groups (patch and lozenge, 3.6%; bupropion and lozenge, 3.5%; 1.1% placebo). Serious adverse events were infrequent and were not attributed to the use of combined pharmacotherapies in either trial.

Discussion

Our study examined the efficacy of combination pharmacotherapies and pharmacotherapy combined with behavioural therapy for smoking cessation in RCTs with factorial designs. Although we found trends signalling that a possible benefit could be obtained with combination pharmacotherapies, no combination was significantly superior to pharmacological monotherapy.

Findings for behavioural therapy combined with pharmacotherapy were similar across trials (despite a wide range of behavioural interventions), with no significant differences observed in NRT and bupropion trials to suggest that higher support behavioural interventions resulted in improved abstinence, compared to lower support interventions. Safety and adverse event data revealed combination pharmacotherapies resulted in composite adverse

events known to occur with the use of each constituent therapy. Overall, data from the included factorial design RCTs were insufficient to conclude that combination therapy for smoking cessation had superior efficacy relative to pharmacological or behavioural monotherapies.

In contrast to our findings, two previous meta-analyses have suggested that combination therapies may be more efficacious for smoking cessation than monotherapies. In a 2008 meta-analysis of five RCTs, Shah et al.²⁰ reported that combination pharmacotherapy increased abstinence rates from 19.1% to 29.3% at six months (OR 1.54; 95% CI 1.19–2.00) and from 14.3% to 22.2% at 12 months (OR 1.58; 95% CI 1.25–1.99). However, this meta-analysis pooled all combinations versus all monotherapies, preventing the comparison of relative efficacy and tolerability of different combinations and their respective monotherapies. Previous studies have also found modest positive trends in smoking abstinence resulting from combining pharmacotherapy with behavioural therapy. A 2012 Cochrane review by Stead et al.²¹ concluded that pharmacotherapy combined with intensive behavioural intervention resulted in significantly higher smoking abstinence, compared to a minimal intervention or standard of care (risk ratio [RR] 1.82; 95% CI 1.66–2.00). In a second study,²² the same authors found a small but significant benefit when intensive behavioural support was used as an adjunct to pharmacotherapy (RR 1.16; 95% CI 1.09–1.24), relative to a less intensive behavioural intervention.

Evidence supporting combination therapy should be nuanced with additional considerations. Stead et al.²¹ compared pharmacotherapy combined with a behavioural intervention to a minimal intervention or the standard of care. Although results demonstrated that combination pharmacotherapy is superior to a minimal intervention control, the authors did not examine whether combination therapy resulted in increased abstinence relative to monotherapy. The similarity in effect size between this review and those reported in two previous Cochrane reviews examining the efficacy of NRT monotherapy²³ (pooled estimate from 111 trials: RR 1.58; 95% CI 1.50–1.66) and bupropion monotherapy²⁴ (pooled estimate from 36 trials, RR 1.69; 95% CI 1.53–1.85) suggests that the increased abstinence with combination therapy may be minimal, beyond that obtained with monotherapy. In their second Cochrane review,²² only five of 38 studies obtained a significant benefit from increasing the level of behavioural support among participants receiving any pharmacotherapy for smoking cessation. In addition, this relationship was no longer significant in a subgroup of 29 studies with face-to-face contact for control and intervention groups (RR 1.09; 95% CI

0.99–1.19). Overall, the generalizability of the very modest results obtained from increasing the intensity of behavioural interventions in clinical trial conditions remains unclear.

Our systematic review only examined RCTs with factorial designs. By restricting to these designs, we anticipated high-quality studies with an ability to make comparisons between combinations, their respective monotherapies, and a control arm. However, the included studies were likely underpowered to statistically test the interaction between treatment groups. For example, while there was a modest and clinically significant increase in abstinence (5.2%) among patients randomized to the nicotine patch with bupropion, relative to bupropion monotherapy, in the second-largest included trial,⁸ this difference was not statistically significant. In total, five trials^{10,14,15,18,19} included treatment groups with fewer than 100 participants.

High rates of participants lost to follow-up could also have affected the results of individual trials included in our review. In the trial by Jorenby et al.,⁸ high loss to follow-up in both the placebo and nicotine patch arms (48.8% and 37.8%, respectively), compared to the nicotine patch with bupropion arm (26.1%), might have resulted in an overestimate of the difference between placebo and nicotine patch combined with bupropion. In Tonnesen et al.,¹¹ 88% of participants across all groups were lost to follow-up (data stratified by treatment arm were not reported) and were assumed to have returned to smoking, making it improbable that significant differences between groups would be observed. The number of participants lost to follow-up by 12 months was also high in the studies conducted by McCarthy et al.¹⁷ and Levine et al.,¹⁸ in which rates among treatment groups ranged from 32.8% to 38.8% and 46.2% to 58.2%, respectively.

Current practice guidelines^{4,25} propose that combination pharmacotherapies and pharmacotherapy combined with behavioural therapy can significantly increase smoking cessation rates. However, the lack of high-quality data from factorial designs comparing combination smoking cessation therapies to monotherapies is surprising and limits our understanding of the interaction between smoking cessation therapies used concurrently. Thus, although we cannot discount the possibility that some combinations of smoking cessation therapies may be superior to monotherapies, the evidence available to date limits our ability to draw definitive conclusions about the relative efficacy and tolerability of different combinations of smoking cessation therapies.

Limitations

Our study has several potential limitations. First, we were unable to pool included data due to heterogeneity between trials, including a wide range of pharmacotherapies and behavioural therapies studied. Second, there was a lack of power and high rates of participants lost to follow-up among included studies, limiting our ability to draw conclusions based on these data. Lastly, there were no factorial design trials comparing varenicline to smoking cessation therapies.

Conclusion

Data from RCTs with factorial designs are insufficient to recommend combination therapy over monotherapies for smoking cessation. Treatment effects were inconsistent across trials. No combination therapy was found to be significantly superior to monotherapy.

Disclosures

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† Appendices, see pages 54–62

Why I Wrote the New Royal College General Internal Medicine Exam: Redefining Our Identity and Revalidation

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Summary

In 2010, the Royal College of Physicians and Surgeons of Canada (RCPSC) recognized General Internal Medicine (GIM) as a distinct subspecialty. Soon after this recognition came a new written certification exam, the successful completion of which awards the applicant the title of General Internist. For those of us who trained prior to the new status and examination, GIM was the default designation after four years of internal medicine training if a subspecialty was not pursued. What does this new subspecialty status mean for our professional identity, qualifications, and public credibility? Twelve years after my successful completion of the Internal Medicine (IM) certification exams, I voluntarily applied for consideration to write the first RCPSC exam in GIM, without a clear reason why. My reflection on the days leading up to the exam and writing the exam itself led me to understand why I did it. The process addressed my skepticism around designating GIM as a unique subspecialty, and through this I have come to appreciate the need for our profession to embrace revalidation.

I had to be patient. If I didn't allow my eyes to wander, I could briefly catch a glimpse of one taking the jump. I saw three: amazing. I had never seen the salmon run before, nor did I know it was in my backyard. For 16 years I lived in this city in two separate spans of my life. Only today did I take a walk along the Humber River and witness the salmon run, thanks to a chance encounter with our course administrator who taught me about this yearly ritual. It was a welcome distraction from the weight of anxiety about the exam I was here to write in less than 24 hours. I checked myself into the Old Mill for a quiet night's sleep. My kids thought it was the most curious thing that their mom was studying. After all, I had already finished university and had a job. Why would I need to study? I spent the last few months trying to explain why I would voluntarily subject myself to hours of studying, missing precious hours at the pool or on the lake during family vacation time.

Last year, I submitted my application to write the first Royal

College of Physicians and Surgeons of Canada (RCPSC) General Internal Medicine (GIM) certification exam. I was a true skeptic. I did not buy into the idea that GIM was unique from Internal Medicine (IM), so how could there be a valid exam distinguishing the two specialties? "You should write the exam," was the advice from my senior colleague in the upper echelons of our college. I perceived a conflict of interest. Or was it a warning that ultimately my career and billings would depend on having this new designation of General Internist to validate my credentials? No one knew. But I do know that I won't do something "just because." Nor did I believe I would suddenly lose my job because I didn't have the new certification. If I did not write and pass, however, I would have to order new business cards that reflected my new identity, dropping the "General" from General Internist. However, if my family and friends are any indication, my patients are equally unaware of the distinction between IM and GIM, and so whether I would

lack credibility with the public was doubtful.

My professional identity is a subject I have thought a lot about since the new subspecialty designation. What makes my knowledge and skills unique from other subspecialists who occasionally practice GIM? I took it as a challenge to find out. I begrudgingly completed the 15-page application for credentials assessment, justifying that the last decade of attending on an academic clinical teaching unit and directing the internal medicine clerkship at my site qualified me for taking the GIM exam. I read through the 22-page objectives and identified areas of knowledge gaps; some of these were because my practice does not include maternal medicine and critical care and some because of the natural evolution of medical information in topics such as new oral diabetes medications, novel oral anticoagulants, updated guidelines, Choosing Wisely campaign recommendations, etc. I realized this was an opportunity to review my knowledge since the time I completed my residency. I will openly confess I enjoyed it. I made study notes. I learned some new things and remembered others that I knew but hadn't used in over a decade. I realized that some skills I have and use daily I had assumed everyone had, but they are indeed unique to GIM. I felt smarter with my trainees. And I convinced myself the objectives of the GIM exam covered a knowledge base distinct from the core internal medicine exam.

That day by the river, watching the salmon run, I was extremely anxious. I didn't have enough time to cover all the material I wanted. I neglected critical care. What if I didn't pass? What if my writer's cramp was psychosomatic and I become unable to write out answers from fear of failure? What if I am really an imposter? Somehow, the surprise salmon at the river made me forget this anxiety.

When the time came and I lined up to register, I saw many familiar faces, including trainees I had worked with, administered practice oral exams for, and now lined up with to write their subspecialty exams. "Dr. Abdullah? What are you doing here?" It was uncomfortable, for sure. How do I explain that I did actually pass my exams 12 years ago, that I was a legitimate internist, and that I wasn't deceiving them? "I'm writing the GIM exam; it's new." "No, not everyone is doing this." "Why? I don't know why I'm writing."

"You're brave," was one response reminiscent of my colleagues' comments when they found out my crazy plan. Am I the only one? I was relieved to see three other brave colleagues of mine from another hospital, eagerly waiting in line behind me, pencil cases in hand.

It was a long exam. My writer's cramp crept up at the end of three hours. I was tired of writing, not anxious. The pragmatic exam was actually a great synopsis of everyday practice. There

were some ridiculously easy questions and one or two complete write-offs, but the majority were good questions. I left feeling a sense of professional and personal accomplishment. I now know the real answer to why I did it. I had ignored opinions that I didn't need to study for this exam, mostly out of fear of failure. After writing, I have no doubt I would have passed without studying, but for me the goal was not simply to pass; it was voluntary revalidation.

As adult learners, I don't see it as problematic for an exam to drive our learning; it is essential. If it is a well-written exam that tests what we should know, then what better way to periodically evaluate our knowledge and ensure we remain up to date? I agree with Levinson:¹ Canada should follow the American model of revalidation for all physicians every 10 years. Canada does not yet have an external revalidation process for physicians. Although there are many potential tools that could be implemented into clinical practice, the most we have for our specialty is our college maintenance of certification program, which relies on self-assessment. Writing the GIM exam could be just one component of a more comprehensive recertification program for GIM. Similar to the American Board of Internal Medicine exams, it would bring us one step closer to a legitimate revalidation process that the public deserves.

Word has spread. The residents now come to ask, "Wow, did you really do it?" They think it is remarkable that their attending would study and write another RCPSC exam. We can all be great role models of true lifelong learning, setting periodic personal learning objectives, and not fearing revalidation.

My kids still look forward to doing homework because mommy will be sitting down with them studying, too. I have set new objectives for the next year and it has become a part of daily life. Until I retire, there will always be the next patient who is unique, and I will learn something new from them. And just maybe, along the way, I will learn something interesting and unrelated, like I did with the salmon run. I can say with confidence to my patients and trainees, that I am a General Internist.

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Hemophagocytic Lymphohistiocytosis Associated with Adult Vaccination: A Case of Cytokine Flurries

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Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is an often-fatal condition characterized by an overactive but ineffective immune response. Secondary HLH in adults is often caused by infection, autoimmune disease, and malignancy. A 67-year-old woman presented to hospital with a five-day history of malaise beginning hours after receiving influenza and pneumococcal vaccinations. Her medical history was significant for rheumatoid arthritis, controlled with methotrexate and prednisone. In hospital, she was found to have a new febrile pancytopenia that persisted despite empiric antibiotics and discontinuation of methotrexate. The patient did not have any additional clinical or laboratory evidence of an infectious focus or rheumatoid arthritis flare. She had splenomegaly, but there was no definitive evidence of malignancy. Further testing revealed hepatitis, coagulopathy, and an elevated ferritin. Bone marrow biopsy demonstrated hemophagocytosis, and a diagnosis of HLH was made. She was successfully treated with a modified HLH 94 protocol, using dexamethasone and etoposide. Unfortunately, following hospital discharge after being well for 18 months with no HLH relapses, the patient was diagnosed with anaplastic T-cell lymphoma. HLH was likely secondary to a two-hit process with vaccinations in the context of immune dysregulation secondary to rheumatoid arthritis and subclinical lymphoma. To the best of our knowledge, vaccinations have not been linked to adult HLH; therefore, this case illustrates a potentially novel association in a susceptible patient. We propose that HLH should be considered in all patients with unexplained fever and cytopenias, and diagnosis should prompt evaluation for underlying causes, including vaccinations.

Résumé

La lymphohistiocytose hémophagocytaire est une affection souvent fatale, caractérisée par une réponse immunitaire exagérée, mais inefficace. La LH secondaire chez l'adulte est causée la plupart du temps par une infection, une maladie auto-immune ou une tumeur maligne. Voici le cas d'une femme de 67 ans qui se présente à l'hôpital après cinq jours de malaise à la suite de la vaccination antigrippale et antipneumococcique. L'anamnèse met en évidence une polyarthrite rhumatoïde stable grâce au méthotrexate et à la prednisone. À l'hôpital, elle connaît un épisode de pancytopenie fébrile qui persiste en dépit d'une antibiothérapie empirique et de l'arrêt du méthotrexate. L'investigation ne révèle aucun autre signe clinique ou biochimique d'un début d'infection ou d'une poussée de polyarthrite rhumatoïde. On note une splénomégalie, mais pas de signes concluants de tumeur maligne. Les analyses subséquentes révèlent une hépatite, une coagulopathie et une élévation de la ferritine. À la biopsie de la moelle osseuse, on observe une hémophagocytose, et le diagnostic de LH est posé. La patiente se rétablit grâce au traitement adoptant le protocole HLH 94 modifié faisant appel à la dexaméthasone et à l'étoposide. Elle sort de l'hôpital, mais, malheureusement, après 18 mois de stabilité sans rechute de la LH,

on lui diagnostique un lymphome anaplasique à grandes cellules. La LH découlait probablement d'un processus à deux facettes, soit la vaccination dans un terreau de dérèglement immunitaire en raison de la polyarthrite rhumatoïde et d'un lymphome subclinique. Pour autant que nous sachions, rien ne liait jusqu'à maintenant la vaccination à l'apparition de la LH chez l'adulte; le présent cas serait le premier à révéler un tel lien chez une personne sensible. Nous proposons d'envisager la possibilité d'une LH dans tous les cas de fièvre et de cytopénie inexpliquées, et le diagnostic devrait s'accompagner de l'évaluation de la cause sous-jacente qui pourrait être la vaccination.

Case

A 67-year-old woman with long-standing rheumatoid arthritis presented to hospital with a five-day history of malaise. Her symptoms began within hours following influenza (Vaxigrip – 2012 inactivated influenza vaccine trivalent types A and B) and pneumococcal (Pneumovax 23 –23-valent polysaccharide) vaccinations. She had received influenza vaccinations without incident in the past; however, this was her first pneumococcal vaccination exposure. She was febrile (maximum oral temperature 38.9°C) but otherwise hemodynamically stable with no apparent infectious focus or rheumatoid flare. Physical examination suggested chronic rheumatoid arthritis in her hands and feet. In addition to rheumatoid arthritis, her medical history was significant for hypertension, osteoporosis, and bilateral hip replacements. Home medications included methotrexate, prednisone, folic acid, alendronate, trandolopril, oxycodone, and amitriptyline. She had been taken off subcutaneous methotrexate one year earlier because of leukopenia. She was restarted after a rheumatoid flare and had since been stable with

no further cytopenias on methotrexate 25 mg injected weekly.

Laboratory investigations in hospital revealed a mild chemical hepatitis (AST 270 U/L, ALT 201 U/L, ALP 224 U/L) and pancytopenia (hemoglobin 88 g/L, leukocyte count $0.8 \times 10^9/L$, platelets $44 \times 10^9/L$, neutrophils $0.32 \times 10^9/L$, lymphocytes $0.35 \times 10^9/L$, monocytes $0.12 \times 10^9/L$). Ferritin was $35\,856 \mu\text{g/L}$ with a CRP and ESR of 54.3 mg/L and 8 mm/hr, respectively. Creatinine peaked at $186 \mu\text{mol/L}$. Septic workup and extensive laboratory testing for viral infection (EBV, HIV, CMV, parvovirus, HAV, HBV, HCV, HSV, varicella, measles), was negative, with the exception of a positive hepatitis B core antibody. Follow-up hepatitis B “e” antigen, hepatitis B “e” antibody, and hepatitis B DNA viral load were not detected. Subsequently, the core antibody result was determined to be a false positive. Imaging including computed tomography (CT) scan of the thorax, abdomen, and pelvis showed splenomegaly. Previous abdominal ultrasound described a spleen within normal limits. Blood work from one month earlier showed a chronically elevated CRP but was otherwise unremarkable.

Figure 1. Bone marrow biopsy demonstrating hemophagocytosis. Black arrows show reactive histiocytes with phagocytosis of red blood cells and platelets.

Broad-spectrum antibiotics were initiated and methotrexate was stopped. However, the patient continued to be febrile, without improvement in her blood counts. This was accompanied by a significant decrease in fibrinogen and an elevated INR. Despite this, two and a half weeks after the onset of her symptoms, she remained clinically well with only minimal fatigue and no major complications. Hematology was consulted and a bone marrow biopsy showed hemophagocytosis. Bone marrow was very weakly positive for T-cell clonality by PCR; however, CT imaging and physical exam did not reveal any clear evidence of malignancy. Her clinical presentation of fever, splenomegaly, hypofibrinogenemia, pancytopenia, hepatitis, elevated ferritin, and hemophagocytosis met criteria for the diagnosis of hemophagocytic lymphohistiocytosis (HLH).

She was initially managed supportively and then started on a modified HLH 2004 protocol with dexamethasone and etoposide for eight weeks. Rapid clinical and biochemical improvement was observed, accentuated by a ferritin decrease of over 50% within two days. Her blood counts steadily improved and reached baseline levels over three months.

The patient had regular hematology follow-up, and despite no relapses of HLH, 18 months after initial presentation was diagnosed with anaplastic T-cell lymphoma (ALK-). This was discovered incidentally on ultrasound evaluation for leg swelling. It is suspected that she had clonal lymphoid hematopoiesis at the time of HLH; however, investigations as described above did not reveal clear evidence of lymphoma at that time.

Overall, HLH was likely secondary to a two-hit process, with vaccinations triggering HLH in the presence of immune dysregulation secondary to rheumatoid arthritis and subclinical T-cell lymphoma.

Discussion

HLH, also known as hemophagocytic syndrome, is an inflammatory disorder characterized by an overactive but ineffective immune response. Impaired T and natural killer cell cytotoxicity prevents down-regulation of the immune response, leading to sustained histiocytosis and cytokine elevation. Defects in the immune cascade may be genetic (primary) or acquired (secondary), with primary HLH almost exclusive to young children.¹ HLH in adults has been associated with various triggers, including infection, autoimmune disease, malignancy, and medications.²

The clinical picture of HLH is typically non-specific. Common findings include fever, fatigue, hepatosplenomegaly, rash, and neurological symptoms ranging from headache to meningismus.¹ Hemophagocytosis is not pathognomic for HLH and might also be found in other conditions, including blood transfusions and

infections.^{1,3} A retrospective pediatric study showed high ferritin levels (greater than 10,000 µg/L) to be highly specific for HLH. The 2004 HLH diagnostic criteria include eight common clinical and laboratory findings (Table 1), but have never been tested in an adult population. The criteria also incorporate laboratory tests not commonly available.² Lack of definitive diagnostic criteria and the nonspecific clinical picture make the diagnosis of HLH challenging in adults.

Once diagnosed, identifying the trigger can have implications for both treatment and prognosis. Infection-associated HLH may have a milder course, in particular compared to patients with underlying malignancy.^{4,5} Overall, HLH is very aggressive, with a mortality rate as high as 72% in an adult case series.⁶ Early treatment should be directed against both the underlying cause and the immune response. The HLH 2004 protocol for primary HLH uses an eight-week course of dexamethasone, etoposide, cyclosporine, and methotrexate plus stem cell transplant and continuation therapy for refractory patients.⁷ Combinations of glucocorticoids, IVIG, biologics, and etoposide have been used with success in adults with secondary HLH.²

A wide range of microorganisms, including influenza viruses, have been linked to HLH, with EBV being the most common implicated virus.^{1,8} Autoimmune HLH, a similar disease to macrophage activation syndrome, predominately occurs with systemic lupus erythematosus (SLE) and adult Still's disease but has also been documented in rheumatoid arthritis. In the setting of autoimmune disease, HLH primarily occurs at diagnosis or with concomitant infection.⁹ Medications including biologics, antibiotics, anticonvulsants, and methotrexate have also been implicated as triggers.

Table 1. Adapted HLH 2004 Diagnostic Criteria. Molecular evidence of HLH or the presence of five of eight criteria establishes a diagnosis of HLH.⁷

HLH Diagnostic Criteria
Fever $\geq 38.5^{\circ}\text{C}$ for 5 days
Splenomegaly
Cytopenias (affecting at least 2 lineages)
Hemoglobin < 90 g/L
Platelets $< 100 \times 10^3/\text{mL}$
Neutrophils $< 1 \times 10^3/\text{mL}$
Hypofibrinogenemia (< 1.5 g/L) or Hypertriglyceridemia (fasting levels ≥ 2 mmol/L)
Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
Low or absent natural killer cell activity
Serum Ferritin ≥ 500 µg/L
Soluble CD25 ≥ 2400 U/ml

Lymphoma is the most frequent malignant etiology, and ALCL is commonly linked to HLH.² In this setting, the diagnosis of ALCL is predominately made concurrently with that of HLH and associated with malignant bone marrow invasion.¹⁰ In our case, the presence of T-cell clonality on bone marrow PCR suggests occult ALCL at the time of presentation. While the long delay between HLH and the development of overt lymphoma is unusual, treatment with etoposide might have obscured the diagnosis. Etoposide can also lead to secondary malignancies, but the risk is low at cumulative doses under 1200 mg/m², and secondary T-cell lymphoma following etoposide is rare.¹¹ Little is known about the occurrence of HLH following immunizations, but in children, cases have been observed.^{12,13} Furthermore, a cutaneous histiocytic reaction with a similar pathophysiology to HLH was observed in a woman after having pneumococcal vaccination.¹⁴

To the best of our knowledge, there are no documented cases of HLH associated with vaccination in adults. Although immune dysregulation secondary to rheumatoid arthritis and subclinical ALCL likely contributed to her presentation, both lymphoma and autoimmune associated HLH almost always occur in the presence of overt disease exacerbations. The development of our patient's symptoms immediately following vaccination, and the absence of HLH relapse despite persistent lymphoma and rheumatoid arthritis, suggests immunizations as a triggering factor. This unique case of HLH identifies a potential association with immunizations in a susceptible patient.

In summary, HLH should be considered in all adults with unexplained febrile cytopenias. Diagnosis prompts aggressive therapy and a thorough evaluation for underlying causes, including recent vaccinations. Lastly, our case highlights the importance for extended follow-up and malignancy monitoring in HLH patients.

Conflict of interest: none declared.

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A *Streptococcus Intermedius* Brain Abscess Causing Obstructive Hydrocephalus and Meningoventriculitis in an Adult Patient With Chronic Granulomatous Disease

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Abstract

An inherited abnormality of phagocytosis, chronic granulomatous disease (CGD), represents an immunodeficiency characterized by recurrent infection and granuloma formation due to a genetic defect in NADPH oxidase. The 36-year-old male patient with CGD described in this case featured a brain abscess due to *Streptococcus intermedius* infection, complicated by meningoventriculitis and obstructive hydrocephalus. His condition was managed with broad-spectrum antibiotics, interferon gamma-1b, and bilateral external ventricular drains. This report addresses a particular paucity in the literature involving *Streptococcus intermedius* central nervous system infection in the adult CGD population.

Résumé

Anomalie héréditaire de la phagocytose, la granulomatose septique chronique est une forme d'immunodéficience caractérisée par des infections récurrentes et la formation de granulomes, due au déficit d'une enzyme, la NADPH oxydase. L'homme de 36 ans dont il est question ici est atteint de cette maladie et présente un abcès cérébral découlant d'une infection à *Streptococcus intermedius*, compliqué d'une ventriculite et d'une hydrocéphalie obstructive. Le traitement consiste en l'administration d'antibiotiques à large spectre et d'interféron gamma-1b et en la mise en place d'un drainage ventriculaire externe. L'article éclaire un sujet rarement abordé dans la littérature, celui de l'infection cérébrale à *Streptococcus intermedius* chez l'adulte atteint de granulomatose septique chronique.

Introduction

Chronic granulomatous disease (CGD) is an uncommon inherited immunodeficiency that is typically characterized by a lifelong recurrence of severe bacterial and fungal infections. This disorder, inherited as either an autosomal recessive or X-linked trait, is due to a genetic defect in the phagocytic NADPH oxidase complex. Consequently, these phagocytes display inadequate clearance of ingested microorganisms due to an impaired “respiratory burst.” This oxygen consumption surge is intended to generate superoxide and downstream oxygen derivatives, including hydrogen peroxide, a process of antimicrobial oxidation inherent to normal phagocytosis. This impairment in innate immunologic defense owes to the life-threatening infections and granuloma formations in CGD.^{1,2}

The prominent sites of infective and granulomatous involvement in CGD are the lungs, skin, lymph nodes, gastrointestinal tract, and liver. The recurrent infections in CGD are most commonly due to the pathogenic microorganisms *Streptococcus anginosus* group, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Candida species*.^{3,4}

There is scarce documentation of central nervous system (CNS) infection in CGD patients, particularly in adults. Although most cases of CGD-associated CNS infection are attributable to fungi, there is a relative absence of reports of streptococcal CNS infection in the CGD population. One such streptococcal species of the *Streptococcus anginosus* group (previously recognized as the *Streptococcus milleri* group), *Streptococcus intermedius*, is no exception.^{5,6}

The following report describes the case of a 36-year-old male CGD patient with a *Streptococcus intermedius* brain abscess, the complications of which included ventriculomeningitis and obstructive hydrocephalus. We also explore the literature around CNS infection and brain abscesses, with respect to CGD and *Streptococcus intermedius*.

Case

A 36-year-old man with CGD presented to an emergency centre with a one-day history of progressive headache, neck pain, chills, nausea, and myalgia. He was feeling well prior thereto, having just returned a few days beforehand from a one-week trip to Las Vegas, which featured an uneventful stay apart from heavy alcohol consumption (an otherwise occasional drinker). He reported no sick contacts or animal exposures and was otherwise dealing with chronic sinus congestion.

His X-linked CGD has made for a history of recurrent pneumonia (and previously treated for fungal and mycobacterial infections) and bronchiectasis, in addition to granulomatous

colitis and proctitis, several years ago. His first CGD-related infection involving *Pseudoallescheria boydii* pneumonia and osteomyelitis of the ribs and spine (leading to a thoracic resection and engendering a kyphotic spine) was in fact detailed in a previous case report.⁷ He has, however, been free of CGD-related infection in the few years before presentation, including the absence of a regular cough or constitutional symptoms. His only medications were for infection prophylaxis (trimethoprim/sulfamethoxazole 160 mg/800 mg taken orally, twice daily; itraconazole 200 mg orally, once daily; and interferon gamma-1b 82 mcg subcutaneously, three times per week). The patient admitted to inconsistent medication adherence during the months prior to presentation. His medical history was otherwise remarkable for the following chronic issues: gastroesophageal reflux disease, dyslipidemia, hyperuricemia, sinusitis, folliculitis, and benign nephrosclerosis (with microalbuminuria) secondary to previous amphotericin B use. He was working as a teacher and had no recent sexual contacts. He was neither a smoker nor an intravenous drug user. His family history revealed a brother who had died from CGD-related complications.

His initial physical examination (recorded at another hospital) illustrated an alert and oriented man who did not appear toxic or in distress. His vital signs were as follows: temperature 36.5°C, blood pressure 110/70 mmHg, heart rate 80 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation of 91% on room air (97% on two litres per minute of oxygen by nasal prongs). He reported pain with neck movement, though there was no neck rigidity. Kernig’s and Brudzinski’s signs were negative. His cranial nerves were normal on examination, as were his motor, sensory, and coordination systems. He featured an unremarkable precordial exam and palpable, regular peripheral pulses. His respiratory exam illustrated a kyphotic thorax with left-sided crackles on auscultation (a long-standing physical finding). His abdomen was soft, non-tender, and negative for organomegaly. He had no active joints.

His serum laboratory investigations were normal, including his complete blood cell count (hemoglobin, white blood cells, and platelets), electrolytes, and tests for liver function, renal function, inflammation, and coagulation. His chest X-ray illustrated right-greater-than-left reticulonodular opacification (resolved days later). His initial cerebrospinal fluid (CSF), drawn from a lumbar puncture (LP), was turbid and revealed (findings confirmed by tests at another hospital) elevated white blood cell count 10.3×10^6 cells/L (95% polymorphonuclear neutrophils), elevated protein 5.3 g/L and low glucose < 0.07 mmol/L. This initial CSF sample featured a normal cryptococcal antigen test, negative polymerase chain reaction (PCR) tests (for meningococcus, pneumococcus, and herpes simplex virus

[HSV]), negative cultures (bacterial, fungal, mycobacterial), and a negative India ink stain test.

Initial broad-spectrum antibiotic coverage for the patient's newly diagnosed meningitis included meropenem 2 g IV Q8H (for *Pseudomonas*, *Burkholderia*, and community-acquired organisms), vancomycin 1 g IV Q12H (for beta-lactam-resistant pneumococcus and *Staphylococcus aureus*), ampicillin 2 g IV Q4H (for *Listeria*), trimethoprim/sulfamethoxazole 320/1600 mg IV Q6H (for *Nocardia*), and voriconazole 260 mg IV Q12H (for *Aspergillus* and *Scedosporium*).

Four days after admission, the patient demonstrated a mild depression in his level of alertness, prompting a computed tomography (CT) scan of his head (which revealed a ring-enhancing lesion in the corpus callosum) and a repeat LP (which revealed an elevated opening pressure of 39 mmHg). On day six, his level of consciousness deteriorated and was followed by respiratory failure and a generalized tonic-clonic seizure, requiring intubation and transfer to the intensive care unit (ICU). A repeat CT scan of his head illustrated bilateral hydrocephalus and uncal herniation. He was given a small volume of mannitol, and the neurosurgery service was consulted. A right external ventricular drain was inserted, but resulted in neither ventricular decompression nor an improvement in the patient's clinical status. A second ventriculostomy was therefore performed on the left lateral ventricle. With bilateral external ventricular drains in place, the patient's neurologic state improved.

Magnetic resonance imaging of the patient's head on day eight revealed successful decompression of the lateral ventricles. It also allowed for better characterization of the initially observed corpus callosum lesion on CT. It highlighted a cystic mass consistent with an abscess (measuring 2.7 cm biconically, 3.0 cm anteroposteriorly, and 1.5 mm rostrocaudally) in the splenium, along the posteroinferior aspect of the corpus callosum, which had ruptured into the trigone of the left lateral ventricle. This abscess was due to a *Streptococcus intermedius* infection, confirmed by a PCR-positive result of the ventricular CSF and of the stereotactically biopsied abscess, via a left parietal burr hole. Interferon gamma-1b was eventually started on day ten to enhance the patient's immunologic defense, until he was later transferred from the ICU to the neurosurgical ward, after which he was continued back on trimethoprim/sulfamethoxazole, itraconazole, and interferon gamma-1b antimicrobial prophylaxis.

Discussion

The patient in this case report typifies the lifelong recurrence of infections with which CGD patients struggle. The life-threatening nature of his most recent infection involving a brain abscess, as described here, was ascribed to two severe

complications: obstructive hydrocephalus (mass effect) and meningoventriculitis (communication with the ventricular system).

The genetic defect in NADPH oxidase in CGD phagocytes (including macrophages, neutrophils, and monocytes) confers an impaired microbicidal oxidative burst due to limited superoxide and hydrogen peroxide generation. Accordingly, CGD patients are thought to be more susceptible to catalase-positive organisms that can degrade both phagocytic and pathogenic hydrogen peroxide. Conversely, CGD patients are generally not prone to infection by catalase-negative organisms (e.g. *Streptococcus*), as they do not degrade their own hydrogen peroxide, which is eventually supplied to CGD phagocytes as bactericidal reagents. The notion of catalase-dependent virulence in CGD is, however, dependent on hydrogen peroxide production. *Streptococcus intermedius*, a catalase-negative organism, may be pathogenic in CGD because it does not produce hydrogen peroxide.^{4,5,8}

Although *Streptococcus intermedius* is a commensal organism, its pathogenicity often involves purulent infections. While it has been more commonly described in the context of liver abscesses,^{9,10} several reports have detailed brain abscesses due to *Streptococcus intermedius* infection in adult^{11–19} and pediatric^{18,20–26} immunocompetent patients. In regards to immune-compromised hosts, there is one published report of HIV27 and only one report of CGD-associated²⁸ *Streptococcus intermedius* brain abscess to our knowledge.

In spite of the scarcity of CGD-associated CNS infection due to *Streptococcus intermedius* in the literature, there are reports of CNS infections due to other organisms in (predominantly pediatric) CGD patients. The overwhelming majority of such reports involve *Aspergillus* CNS infections with and without abscesses.^{29–38} Several cases have described CNS infections complicated by obstructive hydrocephalus in CGD pediatric patients,^{33,39–41,45} but we found only one other report in the literature of obstructive hydrocephalus in an adult CGD patient.¹⁶ Other previously described cases of CNS infection in CGD patients involve tuberculosis,⁴¹ *Salmonella*,^{42,43} *Phaeoacremonium parasiticum*,⁴⁴ *Alternaria infectoria*,⁴⁵ and *Scedosporium prolificans*.⁴⁶

Conclusion

This case adds to the available literature on CGD that is especially scarce in adult reports of *Streptococcus intermedius* CNS infection. This example of CGD-related infection reinforces the priority for early, aggressive intervention in light of the significant risk of rapid deterioration. It also emphasizes the precariousness of non-adherence to prophylactic pharmacotherapy. Furthermore, it underlines the importance of

isolating the pathogen in a situation where an infected immune-compromised host typically exhibits atypical microbiology.

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Eosinophilia with Granulomatosis and Polyangiitis in a 57-Year-Old Man with Worsening Muscle Pain

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Abstract

Eosinophilia with granulomatosis and polyangiitis (EGPA, previously called Churg-Strauss syndrome or allergic granulomatosis and angiitis) is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis affecting small-sized vessels, which typically occurs in patients with a history of allergic rhinitis or asthma. The most serious cases arise from the involvement of other organ systems, notably the cardiovascular system. Importantly, patients may first exhibit non-specific manifestations such as malaise, fever, anorexia, and weight loss. This variable presentation and the potential for multi-organ involvement can lengthen time to diagnosis and delay treatment.

We describe a patient who presented with progressive myalgias on the background of recently diagnosed rhinosinusitis who was ultimately diagnosed with EGPA. This case is meant to alert general internists to the diagnostic challenges of EGPA.

Résumé

La granulomatose éosinophilique avec polyangéite (anciennement, le syndrome de Churg et Strauss ou angéite allergique granulomateuse) est une vasculite liée à des anticorps anticytoplasme des polynucléaires neutrophiles (ANCA) qui touche les petits vaisseaux sanguins, apparaissant chez des personnes ayant des antécédents de rhinite allergique ou d'asthme. Les cas les plus graves surviennent quand la vascularite s'étend à d'autres systèmes organiques, plus particulièrement au système cardiovasculaire. Il est important de noter que les premières manifestations peuvent être d'ordre général, comme un malaise, de la fièvre, de l'anorexie et une perte de poids. En raison de ce tableau clinique variable et de la possibilité de l'atteinte multiorganique, le diagnostic peut être long à établir, ce qui risque de retarder le traitement.

Case

A 57-year-old man presented to the emergency department with worsening muscle pain of the lower extremities, bilaterally. The patient had been well until approximately two weeks prior to presentation, when he noticed a deep ache in his thighs with activity and a precipitous decline in performance as goalie in his recreational hockey league ("I was letting in too many goals"). The pain became more severe, affecting his daily physical functioning; soon the discomfort prevented him from standing for more than 15 minutes at a time. He subsequently developed migratory swelling and pain, first affecting the right heel, then moving to the right wrist, the plantar aspect of his left foot, and the left knee. He began experiencing intermittent drenching night sweats and endorsed a recent weight loss of about 6 kg. Finally, he developed bilateral shoulder and jaw pain that prompted him to seek medical attention by presenting to hospital.

His medical history included chronic rhinosinusitis with polyposis, diagnosed endoscopically 10 months earlier, for which he was taking inhaled budesonide and formoterol twice daily and mometasone furoate monohydrate intranasally as required. He did not have a history of asthma. He took no other medications.

The physical exam revealed vital signs, including temperature, that were within normal limits. Examination of his lower and upper limbs revealed no objective weakness and the neurological exam was normal. His gait was antalgic bilaterally and he was unable to hold his arms above his head secondary to pain. Respiratory exam was normal, musculoskeletal examination demonstrated no active joints, and there was no rash. He was admitted to hospital for further workup and management.

Initial blood work was significant for an elevated white blood cell count at $20.44 \times 10^9/L$, with a differential revealing an eosinophil level of $9.61 \times 10^9/L$. Electrolytes and creatinine were within normal limits. Testing of inflammatory markers revealed an erythrocyte sedimentation rate of 25 mm/hr and a C-reactive protein of 82.9 mg/L. Creatine phosphokinase (CPK) was mildly elevated at 371 IU/L. Urinalysis showed 2+ blood. Chest radiograph was normal. Serology for parasitic infection and an autoimmune panel were pending.

His muscle pain was treated with naproxen 500 mg orally twice daily. His symptoms improved and he was discharged the following day, with an outpatient rheumatology follow-up appointment in one week. Three days later, he returned to the emergency department with new-onset left foot numbness and interval development of a rash over his legs and scalp. His

muscle pain returned and was significantly worse, affecting nearly his entire upper and lower limbs, with attenuation in the symptomatic relief provided by naproxen. On examination, he had decreased sensation to light touch affecting the left lower limb and evidence of new purpuric lesions on his palms, lower limbs, and dorsum of the feet. He also had blanchable papular lesions on his forehead. Musculoskeletal examination revealed tenosynovitis at the left second to fourth metatarsophalangeal joints. Testing for muscle power was limited secondary to pain. Repeat blood work demonstrated a rising CPK at 1,040. Testing for perinuclear (p)-anti-neutrophil cytoplasmic antibody (ANCA) was positive. Magnetic resonance imaging (MRI) of the lower limbs demonstrated diffuse edema of the musculature bilaterally consistent with myopathy. Nerve conduction and electromyography studies did not show a deficit. Echocardiogram and pulmonary function tests were normal. Chest computed tomography (CT) was subsequently performed and did not suggest active lung involvement. He was initiated on prednisone 60 mg daily with rapid improvement of his myalgias. He was discharged from hospital with plans for close follow-up with a rheumatologist specialized in vasculitis.

Discussion

Eosinophilia with granulomatosis and polyangiitis (EGPA) is a vasculitis of the small-sized blood vessels associated with hyperes eosinophilia and necrotizing granulomatous inflammation.¹ It is a multisystem disorder typically occurring in patients with a history of allergic rhinitis or asthma. It has an incidence of 0.6–6.8 per million per year.² The mean age of diagnosis is 40 years, with no known gender predominance.³ Both vessel inflammation and eosinophilic proliferation are thought to play a role in organ damage, although the exact pathogenesis is not completely understood.⁴

Among the three ANCA-associated vasculidities (EGPA, granulomatosis with polyangiitis, and microscopic polyangiitis), EGPA is the least common.⁵ The most commonly involved organ is the lung, followed by ear, nose, and/or throat (ENT) involvement and skin; other frequently affected systems include the cardiovascular, gastrointestinal, renal, and central nervous systems. Nearly 40% of patients with EGPA have circulating ANCAs, predominantly directed against myeloperoxidase, with a perinuclear staining pattern (p-ANCA).⁶ Different subtypes of disease may exist with clinical characteristics that differ according to ANCA status⁷: patients with ANCA positivity have been found to be more affected with renal disease, mononeuritis, purpura, and alveolar haemorrhage; cardiac involvement, lung infiltration, and systemic manifestations are more frequently seen in patients who are ANCA negative.^{6,8}

The American College of Rheumatology has developed six criteria for the classification of EGPA: presence of asthma; eosinophilia >10%; mononeuropathy or polyneuropathy; pulmonary infiltrate; non-fixed paranasal sinus abnormality; and extravascular eosinophils on biopsy of a blood vessel. The presence of any four or more of the six criteria produces a sensitivity of 85% and a specificity of 99.7% for diagnosis.⁹ Importantly, these criteria were devised as a classification system to distinguish EGPA from other vasculitides, rather than a formal checklist for the diagnosis of EGPA.

The presentation of EGPA is far from uniform. The initial phase can last years and generally involves allergic rhinitis, nasal polyposis and sinusitis, and/or asthma.² This is followed by the occurrence of vasculitic manifestations, such as skin involvement and/or mononeuritis multiplex. Constitutional symptoms are also often present at diagnosis (40–75%), including fever, weight loss, myalgias, and arthralgias.² At diagnosis, 40–75% of patients have skin involvement, most frequently palpable purpura, but other lesions such as cutaneous nodules or papules with an urticarial appearance can be seen.² Other organ systems are also frequently involved. Between 38–77% of patients can have parenchymal lung involvement. Gastrointestinal manifestations, which occur in 20–50% of patients, may include abdominal pain, vomiting, or diarrhea.¹⁰ Cardiac involvement, present in 27–47% of patients, includes cardiomyopathy and eosinophilic pericardial effusion and is of paramount importance to discern due to its heightened association with disease-related morbidity.^{4,11} Up to 27% of patients may have renal involvement, mainly in the form of focal segmental or pauci-immune glomerulonephritis.¹²

The initial and cornerstone of treatment for EGPA is corticosteroids. For patients with evidence of systemic vasculitis, treatment is initiated with prednisone (or equivalent) at a dose of 1 mg/kg per day. Additional immunosuppressive agents are typically added in cases of refractory or severe disease, such as impending respiratory failure, cardiac involvement, glomerulonephritis, and/or severe motor neuropathy. Most patients with EGPA improve with glucocorticoid therapy alone.¹³ Once symptomatic remission has been achieved, the dosage of steroid is gradually tapered over 12–18 months, as tolerated by the patient. However, a report of patients without poor prognosis factors (i.e., no cardiac, renal, or central nervous system involvement) indicated that almost 80% of those who achieved remission required long-term, low-dose glucocorticoid therapy because of lingering asthma or rhinitis.¹³

Conclusion

This was the case of a 57-year-old man with progressive myalgias affecting the upper and lower limbs, associated with weight loss and migratory tenosynovitis, and with a history of allergic rhinitis. Diagnosis only became apparent as the other manifestations of EGPA developed with eosinophilia, skin involvement, and neuropathy. This case highlights the challenges associated with diagnosing EGPA. Given the multi-system and heterogeneous nature of the disease, keeping the diagnosis on one's radar, recognizing its presenting features, and including it in the differential diagnosis is essential.

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Breaking-Out Bad: A Case of Levamisole-Induced Vasculitis

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Summary

The addition of harmful adulterants to cocaine has become widespread in recent years and constitutes a novel etiological agent for disease. One agent in particular, the veterinary anthelmintic “levamisole,” has been increasingly used, owing to its potentiating effects of cocaine and its ability to pass crude methods of detection. Levamisole has been shown to cause a vasculitic syndrome of retiform purpura and skin necrosis, as well as leukopenia and autoantibody formation.

Résumé

L'ajout d'adultérants nocifs à la cocaïne s'est répandu dans les dernières années, à tel point que ces produits sont devenus de nouveaux agents étiologiques de maladies. L'un de ces agents en particulier, l'anthelminthique d'usage vétérinaire lévamisole, est de plus en plus utilisé pour son effet potentialisateur de celui de la cocaïne et parce qu'il n'est pas détecté par les méthodes de dépistage élémentaires.

Introduction

We present the case of a 56-year-old man with a history of “crack” cocaine with levamisole-induced vasculitis (LIV), confirmed by detection in the urine. He exhibited classic features of LIV, including purpuric rash over the ears, mild leukopenia, and significantly elevated cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA), with biopsy features of leukocytoclastic vasculitis. The patient was counselled to abstain from cocaine use and was treated with daily prednisone. Following a week, his symptoms rapidly improved.

This case highlights the clinical features, investigations, and management of a patient with LIV. It is important for health care practitioners to be able to recognize this disease phenomenon and gain familiarity with its diagnosis and treatment.

Background

Cocaine is the second most commonly used illicit substance in Canada. Its use has been linked to a variety of autoimmune syndromes that vary widely in clinical presentation and distribution.^{1,2} Moreover, the addition of harmful potentiating

substances to cocaine, such as levamisole, a veterinary anthelmintic agent banned for human use, has become increasingly widespread and constitutes a novel etiological agent for disease.³ We present a case of levamisole-induced vasculitis (LIV) and discuss its clinical features, diagnostic work-up, and management.

Case

A 56-year-old white man with a history of intravenous drug use⁴ (IVDU), chronic hepatitis C infection, type 2 diabetes mellitus, hypothyroidism, and major depressive disorder with a five-year history of increasing “crack” cocaine use presented to the emergency department with a two-month history of purpuric painful lesions. They were located preferentially on his inner thighs and knees, the posterior surfaces of his arms, and over his ears, the latter location being where they first appeared. He also endorsed a three-week history of a 10-pound unintentional weight loss, night sweats, chills, and diffuse arthralgia.

The patient's medications included metformin, gliclazide, ramipril, and citalopram. He had last smoked “crack”

cocaine four days prior. He had a known drug allergy to fluoroquinolones and hypersensitivity to alcohol. He denied any recent sick contacts, new sexual partners, or recent travel. Review of systems was negative.

On examination, the patient appeared well. He was afebrile. Examination of the skin revealed purpuric patches on the helices of the ears bilaterally, with regions of overlying frank necrosis and crusting eschars (Figure 1). The lesions were extremely tender on palpation. Large patches of retiform and stellate purpura were located symmetrically over the bilateral triceps, inner thighs, and knees (Figures 2 and 3). No other significant findings were present on physical examination.

On investigation, the leukocyte count was 3.4. The rest of the complete blood count, electrolytes, and liver and renal function tests were unremarkable. Urine dipstick was negative for proteinuria. ANA, RF, HIV screen, and hepatitis B serology were negative. c-ANCA was elevated at 4.3, and perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) was normal. A urine toxicology screen confirmed ingestion of cocaine, levamisole, and citalopram.

A punch biopsy of a skin lesion over the back of the right arm was performed and the histology was in keeping with leukocytoclastic vasculitis. Specifically, fibrinoid necrosis of the blood vessel wall with perivascular neutrophilic infiltrate with occasional lymphocytes, eosinophils, and rare histiocytes, and nuclear dust secondary to karyorrhexis or leukocytoclastia was seen (Figure 4).

The patient was prescribed prednisone 20 mg daily and returned for follow-up in one week's time. During this time he had abstained from cocaine use. There was significant improvement in the appearance of his cutaneous lesions. The lesions had faded in colour and there was less overlying erythema. The patient endorsed pruritis at the sites of the lesions. The 2-x-2-cm necrosed lesion over the left ear helix remained unchanged.

Discussion

Ingestion of cocaine contaminated with levamisole is becoming increasingly recognized as a cause of vasculitis. A 2008 figure estimated that 11% of cocaine used in Canada is contaminated with levamisole, while the number is nearly seven-fold greater in the US.³ At the Hamilton General Hospital, 89% of urine samples (31 of 35) from January through April 2012 sent for confirmation of cocaine were also confirmed positive for levamisole.

Levamisole is currently used as an anthelmintic agent in veterinary medicine; previously, it has been a chemotherapy agent in humans for colon cancer and a treatment for recurrent pediatric nephrotic syndrome. Levamisole was banned in Canada in 2003 due to reports of agranulocytosis.⁴ Levamisole has become widely used as an additive or filler, because it

Figure 1. Patient's left and right ears with retiform purpura and necrotic eschars.

Figure 2. Patient's left and right medial aspect of legs with retiform pupura.

Figure 3. Patient's left and right back of arms.

Figure 4. Histopathological features of levamisole-induced vasculitis

potentiates the effects of cocaine and remains essentially undetectable to crude practices that test the purity of cocaine.

As an immune-modulating agent, levamisole has been shown to alter macrophage chemotaxis and T-cell lymphocyte function, enhance activation and maturation of human monocyte-derived dendritic cells, and inhibit the production of endogenous immunosuppressive factors.⁵ In the brain, levamisole augments dopaminergic and endogenous opioid effects via D1 dopamine receptor upregulation.⁵ Levamisole has been postulated to augment the effects of cocaine via inhibition of monoamine oxidase inhibitor (MAOI) and catechol-O-methyltransferase activity, thus prolonging the presence of catecholamine neurotransmitters in the neural synapses, adding to the reuptake-inhibition effect of cocaine.⁶

LIV is associated with several characteristic clinical, pathological, and serological findings. There is a 4:1 female predominance of clinical manifestations.³ The largest review to date, conducted by Larocque and Hoffman (2012),³ concluded that neutropenia and dermatologic manifestations were the most common findings consistent with LIV. In a recent review, leukopenia and neutropenia were reported among 63% of patients.⁷ With respect to cutaneous findings, lesions over the lower extremities, ears, and face have been reported in 60–80% of patients.⁸ In addition, the rash associated with LIV has typically been described as a retiform purpuric rash, with possible areas of central necrosis.^{3,7,8} On skin biopsy, common findings include leukocytoclastic vasculitis, as evidenced by perivascular inflammatory infiltrates with fibrinoid necrosis; thrombotic microangiopathy; and gross necrosis.^{3,7,8} Serologic findings of LIV include positive ANCA, with up to 90–100% of patients with positive p-ANCA and 50–60% of patients with positive c-ANCA.^{3,7} Other autoantibodies such as antiphospholipid antibody; antihuman neutrophil antibody; and anti-nuclear antibodies (ANAs), including anti-double-stranded DNA and lupus anticoagulant, have also been shown to be associated.^{9,10}

The pathogenesis of LIV is not fully known, although some hypothesize that levamisole may be directly cytotoxic to neutrophils or endothelial cells.¹¹ Other theories suggest it may be a nonspecific immune adjuvant in certain individuals predisposed to autoimmunity, or may induce loss of tolerance to specific autoantigens in a manner that initiates or perpetuates autoimmunity.¹¹ Some previous studies have suggested an underlying mechanism of immune complex-deposition involving Ig antibodies and complement.⁴

In terms of the natural progression of the disease, symptoms are typically self-resolving once exposure to the offending substance is stopped. Certain cases involving significant necrosis, neutropenia, continued cocaine use, or worsening disease despite treatment have been treated with steroids or

other immunosuppressive agents, as well as anticoagulation for thrombotic complications; however, there is no evidence to suggest this portends a better outcome.¹² In the case of severe cutaneous involvement, debridement, grafting, and appropriate management in a burn unit is generally advisable.

Unfortunately, LIV has been shown in studies to have a high recurrence rate.³ Integral to the management of the acute presentation is counselling for the underlying drug abuse. The importance of cessation of cocaine use must be emphasized, in order to ensure recovery. Patients desiring assistance for their drug abuse should be made aware of such resources as addictions counselling services, outpatient clinics, social work services, and support groups.

The case presented here describes a classic presentation of levamisole-induced vasculitis secondary to cocaine use. Cutaneous findings of retiform purpura overlying the helices of the ears, ANCA positivity, and leukocytoclastic vasculitis on skin biopsy are classic findings. A urine levamisole test by gas chromatography-mass spectrometry method confirmed our hypothesis.

The decision to treat with oral prednisone was largely based on the presence of small areas of necrosis, as well as the presence of mild leukopenia. To date, there are no evidence-based guidelines directing health care professionals to treatment options. As noted, although medications can provide short-term resolution in affected individuals, definitive cure and prevention of recurrence necessitates cessation of cocaine use.

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Search	Query
1	MeSH descriptor: [Smoking Cessation] explode all trees
2	MeSH descriptor: [Tobacco Use Cessation Products] explode all trees
3	MeSH descriptor: [Smoking] explode all trees
4	((cigarette*.ti,ab or "tobacco".ti,ab or #3 or "smoking".ti,ab or smoker*.ti,ab) and ("cessation".ti,ab or quit*.ti,ab or stop*.ti,ab))
5	#1 or #2 or #4
6	MeSH descriptor: [Bupropion] explode all trees
7	bupropion:ti,ab
8	zyban:ti,ab
9	amfebutamone:ti,ab
10	budeprion:ti,ab
11	varenicline:ti,ab,kw
12	chamfix:ti,ab
13	chantix:ti,ab
14	("nicotine".ti,ab and (patch*.ti,ab or lozenge*.ti,ab or inhaler*.ti,ab or ("nasal" next spray*.ti,ab) or ("transdermal" next system*.ti,ab) or "gum".ti,ab or "polacrilex".ti,ab or "replacement".ti,ab))
15	nicoderm:ti,ab
16	nicorette:ti,ab
17	habitrol:ti,ab
18	MeSH descriptor: [Behavior Therapy] explode all trees
19	(behavior* next therap*):ti,ab
20	(behaviour* next therap*):ti,ab
21	("cognitive" next therap*):ti,ab
22	MeSH descriptor: [Counseling] explode all trees
23	counseling:ti,ab
24	counseling:ti,ab
25	pharmacotherap*:ti,ab
26	MeSH descriptor: [Combined Modality Therapy] explode all trees
27	("combined" next "modality" next therap*):ti,ab
28	nrt:ti,ab
29	MeSH descriptor: [Psychotherapy, Group] explode all trees
30	psychotherap*:ti,ab
31	psychoeducation*:ti,ab
32	("combination" next therap*):ti,ab
33	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
34	#5 and #33

Search	Query
1	Smoking cessation
2	((cigarette* or tobacco or smoking or smoker*).tw. or smoking/) and (cessation or quit* or stop*).tw.
3	1 or 2
4	amfebutamone
5	bupropion.tw.
6	zyban.tw.
7	amfebutamone.tw.
8	budeprion.tw.
9	varenicline
10	varenicline.tw.
11	chamfix.tw.
12	chantix.tw.
13	(nicotine and (patch* or lozenge* or inhaler* or nasal spray* or transdermal system* or gum or polacrilex or replacement)).tw.
14	nicotine patch
15	nicotine lozenge
16	nicotine gum
17	nicotine replacement therapy
18	nicoderm.tw.
19	nicorette.tw.
20	habitrol.tw.
21	exp psychotherapy
22	behavior?r* therap*.tw.
23	cognitive therap*.tw.
24	exp counseling
25	counsel?ing.tw.
26	pharmacotherap*.tw.
27	combined modality therap*.tw.
28	combination therap*.tw.
29	psychoeducation*.tw.
30	nrt.tw.
31	psychotherap*.tw.
32	or/4-31
33	3 and 32
34	(random\$ or factorial\$ or crossover\$ or cross over\$ or placebo\$ or (doubl\$ adj blind\$) or (singl\$ adj blind\$) or assign\$ or allocat\$ or volunteer\$).tw. or (crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/)
35	33 and 34

Search	Query
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2	((cigarette* or tobacco or smoking or smoker*).tw. or tobacco smoking/) and (cessation or quit* or stop*).tw.
3	1 or 2
4	bupropion
5	bupropion.tw.
6	zyban.tw.
7	amfebutamone.tw.
8	budeprion.tw.
9	varenicline.tw.
10	chamfix.tw.
11	chantix.tw.
12	(nicotine and (patch* or lozenge* or inhaler* or nasal spray* or transdermal system* or gum or polacrilex or replacement)).tw.
13	nicoderm.tw.
14	nicorette.tw.
15	habitrol.tw.
16	exp psychotherapy
17	psychotherap*.tw.
18	exp behavior modification
19	behavio?r* therap*.tw.
20	cognitive therapy
21	cognitive therap*.tw.
22	exp counseling
23	counsel?ing.tw.
24	pharmacotherap*.tw.
25	combined modality therap*.tw.
26	combination therap*.tw.
27	psychoeducation*.tw.
28	nrt.tw.
29	or/4-28
30	3 and 29
31	(placebo*: or random*:).tw. or exp treatment
32	(risk* or search*).tw. or exp treatment
33	31 or 32
34	30 and 33

Search	Query
#44	Search #43 NOT (animals[mh] NOT humans[mh])
#43	Search #42 AND #39
#42	Search (#40 OR #41)
#41	Search (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab])
#40	Search ((systematic review[ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR (systematic review[tiab] AND review[pt]) OR consensus development conference[pt] OR practice guideline[pt] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR drug class reviews[ti]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri*[tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[tiab] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication[tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt] OR comment[pt]))
#39	Search (#7 AND #38)
#38	Search (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37)
#37	Search combination therap*[tiab]
#36	Search psychoeducation*[tiab]
#35	Search psychotherap*[tiab]
#34	Search "Psychotherapy, Group"[Mesh]
#33	Search nrt[tiab]
#32	Search combined modality therap*[tiab]
#31	Search "combined modality therapy"[MeSH Terms]
#30	Search pharmacotherap*[tiab]
#29	Search counseling[tiab]
#28	Search counseling[tiab]
#27	Search "counseling"[MeSH Terms]
#26	Search cognitive therap*[tiab]
#25	Search behavioral therap*[tiab]
#24	Search behavioral therap*[tiab]

#23	Search behaviour therap*[tiab]
#22	Search behavior therap*[tiab]
#21	Search "behavior therapy"[MeSH Terms]
#20	Search habitrol[tiab]
#19	Search nicotine[tiab]
#18	Search nicoderm[tiab]
#17	Search (nicotine[tiab] AND (patch[tiab] OR patches[tiab] OR lozenge[tiab] OR lozenges[tiab] OR inhaler[tiab] OR inhalers[tiab] OR nasal spray[tiab] OR nasal sprays[tiab] OR transdermal system*[tiab] OR gum[tiab] OR polacrilex[tiab] OR replacement[tiab]))
#16	Search chantix[tiab]
#15	Search champix[tiab]
#14	Search varenicline[tiab]
#13	Search "varenicline"[Supplementary Concept]
#12	Search budeprion[tiab]
#11	Search amfebutamone[tiab]
#10	Search zyban[tiab]
#9	Search bupropion[tiab]
#8	Search "bupropion"[MeSH Terms]
#7	Search (#4 OR #5 OR #6)
#6	Search (((cigarette*[tiab] OR tobacco[tiab] OR smoking[mesh] OR smoking[tiab] OR smoker*[tiab]) AND (cessation[tiab] OR quit*[tiab] OR stop*[tiab])))
#5	Search Tobacco Use Cessation Products[Mesh]
#4	Search smoking cessation[MeSH Terms]

Trial	N	Treatment group	n	Treatment Duration	Behavioral intervention in all groups
Piper (2009)	1504	Bupropion / Nicotine lozenge	262	Patch arm for 8 weeks	6 individual counseling sessions for 10-20 minutes
		Nicotine patch / Nicotine lozenge	267		
		Bupropion	264	Patch arm for 8 weeks	
		Nicotine lozenge	260		
		Nicotine patch	262	Lozenge arm for 12 weeks	
		Placebo / Placebo	189		
Jorenby (1999)	893	Nicotine patch / Bupropion	245	Patch arm for 8 weeks	Initial telephone call from counselor, 1 hour of individual counseling per week for 9 weeks
		Placebo patch / Bupropion	244		
		Nicotine patch / Placebo pill	244	Pill arm for 9 weeks	
		Placebo patch / Placebo pill	160		
Tonnesen (2000)	446	Nicotine patch / Nicotine inhaler	115	All treatments 12 weeks	15-minute initial physician counseling session
		Nicotine inhaler	118		
		Nicotine patch	104		
		Placebo patch / Placebo inhaler	109		
Swanson (2003)	131	Nicotine patch / Bupropion	29	All treatments 9 weeks	"Fresh Start" program 1.5 hours once a week for 4 weeks, 5 1-hour support groups
		Bupropion	21		
		Nicotine patch	31		
		No treatment	50		

Trial	N	Pharmacological / Behavioral	n	Length of treatment	Behavioral intervention
Ahluwalia (2006)	755	Nicotine gum / Motivational interview	189	Pill arm x 8 weeks	Health education: current guideline standard counseling (focus on information and advice); Motivational interviewing: counseling for addictive behaviours, scripts exploring pros and cons of smoking/quitting, motivation and confidence to quit.
		Nicotine gum / Health education	189		
		Placebo gum / Motivational interview	189	Counseling x 16 wks	
		Placebo gum / Health education	188		
Killen (1997)	424	Nicotine patch / Manual & video	109	All treatments x 16 wks	Manual: self-help treatment manual; Manual with video: video viewed in a group, then received. Designed to increase manual efficiency. Fictional characters modeled relapse-prevention skills from the manual.
		Nicotine patch / Manual	103		
		Placebo patch / Manual & video	108		
		Placebo patch / Manual	104		
Tonnesen (2006)	370	Nicotine pill / High support	90	NRT x12 wks, ≤12 months	Low-support: 4 visits, and 6 telephone calls (total contact time 2.5 hours); High-support: 7 visits, and 5 telephone calls (total contact time 4.5 hours).
		Nicotine pill / Low support	95		
		Placebo pill / High support	97	Counseling x 12 months	
		Placebo pill / Low support	88		
Hall (1987)	139	Nicotine gum / Intensive	34	NRT ≤12 months	Low contact: 5 60-minute meetings (education about quitting and consequences of smoking). Intensive: 14 75-minute meetings (relapse prevention skill training, and written exercises).
		Nicotine gum / Low contact	34		
		Placebo gum / Intensive	35	Counseling x 12 months	
		Placebo gum / Low contact	36		
Brown (2007)	524	Bupropion / CBTD	108	12 wks	CBT: 12 90-minute sessions over 12 weeks; CBTD: same as CBT, in addition to extra cognitive-behavioral coping skills for depression.
		Bupropion / CBT	147		
		Placebo pill / CBTD	112		
		Placebo pill / CBT	157		
McCarthy (2008)	463	Bupropion / Standard counseling	113	Treatment x 9 weeks	Non-counseling: education regarding medication use with general support. Standard counseling: 2 pre-quit and five post-quit 10-minute sessions (help maintain motivation, preparing to quit, coping, relapse prevention, social support).
		Bupropion	116		
		Placebo pill / Standard counseling	121	Counseling x 4 wks	
		Placebo pill	113		
Levine (2010)	349	Bupropion / Weight concerns	106	Pill arm x 26 weeks	Standard counselling: 12 90-minute group counseling sessions led by clinicians (preparing to quit, benefits of cessation, coping with urges to smoke, and relapse prevention); Weight concerns: additional content tailored to weight concerns.
		Bupropion / Standard counseling	89		
		Placebo pill / Weight concerns	87	Counseling x 12 weeks	
		Placebo pill / Standard counseling	67		
Hall (2002)	146	Bupropion / Psychological	37	Pharmacotherapy x 12 wks	Medical management: 10-20 minute initial visit, 3 5-minute meetings (advice to stop smoking and educational materials); Psychological intervention: medical management as well as 5 90-minute sessions with written exercises.
		Bupropion / Medical management	36		
		Placebo pill / Psychological	36	Behavioral x 11 weeks	
		Placebo pill / Medical management	37		

Abbreviations: CBT = cognitive behavioral therapy, CBTD = Cognitive behavioral therapy for depression, NRT = Nicotine replacement therapy

	Trial	Therapy	n	6 months		12 months	
				Continuous Abstinence (%)	Odds Ratio (CI)	Continuous Abstinence (%)	Odds Ratio (CI)
Pharmacological Combination Trials	Tonnesen (2000)	Nicotine patch / Nicotine Inhaler	115	8.7	1.39 (0.51-3.78)	3.5	1.93 (0.35-10.74)
		Nicotine inhaler	118	5.9	0.92 (0.31-2.71)	5.1	2.87 (0.57-14.51)
		Nicotine patch	104	14.4	2.46 (0.96-6.29)	8.7	5.07 (1.07-24.04)
		Placebo	109	6.4	1.00 (ref.)	1.8	1.00 (ref.)
	Swanson (2003)	Nicotine patch / Bupropion	29	0	-	13.8	0.98 (0.26-3.69)
		Bupropion	21	0	-	4.8	0.31 (0.04-2.67)
		Nicotine patch	31	9.7	-	9.7	0.66 (0.16-2.76)
		No treatment	50	2.0	-	14.0	1.00 (ref.)
Pharmacological and Behavioral Combination Trials	Tonnesen (2006)	Nicotine / High support	90	-	-	14	3.55 (1.11-11.34)
		Nicotine / Low support	95	-	-	14	3.33 (1.04-10.63)
		Placebo / High support	97	-	-	6	1.39 (0.39-5.08)
		Placebo / Low support	88	-	-	5	1.00 (ref.)
	McCarthy (2008)	Bupropion / Counseling	113	30.1	2.13 (1.13-4.02)	20.4	1.55 (0.77-3.12)
		Bupropion	116	25.0	1.65 (0.86-3.15)	18.1	1.34 (0.66-2.72)
		Placebo / Counseling	121	18.2	1.10 (0.56-2.16)	12.4	0.86 (0.40-1.83)
		Placebo	113	16.8	1.00 (ref.)	14.2	1.00 (ref.)
	Levine (2010)	Bupropion / Weight concerns	106	34	4.41 (1.83-10.63)	24	3.83 (1.39-10.57)
		Bupropion / Standard	89	21	2.33 (0.92-5.91)	19	2.93 (1.02-8.40)
		Placebo / Weight concerns	87	11	1.11 (0.40-3.10)	8	1.09 (0.32-3.58)
		Placebo / Standard	67	10	1.00 (ref.)	7	1.00 (ref.)

Abbreviations: CI = Confidence interval, ref. = Reference group

Odds ratio (confidence interval) in comparison to placebo, and using the most rigorous abstinence data available

All studies treated patients lost to follow-up as relapse to smoking

Loss to follow-up calculated as the amount of patients that were randomized in each group less the amount of patients who were successfully followed up

Trial Type	Trial	Sequence generation, randomization	Allocation concealment	Blinding	Incomplete short-term outcome data	Incomplete long-term outcome data	Selective outcome reporting	Other sources of bias
Pharmacological	Piper (2009)	Low	Low	Low	Low	Low	Low	Low
	Jorenby (1999)	Low	Low	Low	Low	Low	Low	Low
	Tonnesen (2000)	Low	Low	High•	Unclear‡	Unclear‡	Low	Low
	Swanson (2003)	Low	Low	High•	Low	Low	Low	Low
NRT and Behavioral	Ahluwalia (2006)	Low	Low	Low	Unclear‡	Unclear‡	Low	Low
	Killen (1997)	Low	Unclear†	Low	Low	Low	Low	Low
	Tonnesen (2006)	Low	Unclear†	Low	Unclear‡	Unclear‡	Low	Low
	Hall (1987)	Low	Unclear†	Low	Low	Low	Low	Low
Bupropion and Behavioral	Brown (2007)	Low	Unclear†	Low	Unclear‡	Unclear‡	Low	Low
	McCarthy (2008)	Low	Low	Low	Low	Low	Low	Low
	Levine (2010)	Low	Unclear†	Low	Low	Low	Low	Low
	Hall (2002)	Low	Unclear†	Low	Low	Low	Low	Low

†Allocation of patients to groups inadequately described

‡Treatment arms of patients lost to follow-up not specified

*Not specified which follow-ups were missed by participants to determine how loss to follow-up would affect results

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- adult patients with type 2 diabetes mellitus in combination with Victoza® (liraglutide) and metformin when Victoza® and metformin do not achieve adequate glycemic control

Levemir® is also recommended in combination with short- or rapid-acting mealtime insulin.

Please consult the product monograph at http://novonordisk.ca/PDF_Files/our_products/Levemir/Levemir_PM_EN.pdf for important information on contraindications, warnings and precautions, adverse reactions, drug interactions and dosing. The product monograph is also available by calling us at 1 (800) 465-4334.

* Comparative clinical significance has not been established.

† Injection Force=the force required to press the push-button on pens to inject insulin.

‡ Adapted from Hemmingsen H *et al.*, 2011. This study compared the injection force of FlexTouch® with that of SoloStar® and KwikPen™. Injection force was measured at 3 constant push-button speeds delivering 80 units with SoloStar® and 60 units with KwikPen™. FlexTouch® was not tested at 3 speeds because the spring-loaded mechanism has no influence on the rate of insulin delivery. Instead, injection force was measured as the spring activation force at 80 units. The manufacturers' recommended needles were used; NovoFine® (Novo Nordisk) 32-gauge tip extra thin wall (etw) 6 mm needle for FlexTouch® and BD (Franklin Lakes, NJ) MicroFine™ 31-gauge 5 mm needle for SoloStar® and KwikPen™. Only one needle of each type was used for all injection force tests to avoid variation in measured injection force caused by the flow stress of different needles.

All products or trademarks are the property of their respective owners.

REFERENCES: 1. Data on file, Telus Health Analytics via Novo Nordisk Canada, 2012. 2. Levemir® Product Monograph, Novo Nordisk Canada Inc., December 2013. 3. Hemmingsen H, Niemeyer M, Hansen MR, Busher D, Thomsen NB. A prefilled insulin pen with a novel injection mechanism and a lower injection force than other prefilled insulin pens. *Diabetes Technol Ther* 2011;13(12):1-5.

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