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“Our starting point is not the individual, and we do not subscribe to the view that one should feed the hungry, give drink to the thirsty, or clothe the naked....Our objectives are entirely different: we must have a healthy people in order to prevail in the world.”

—Joseph Goebbels, Minister of Propaganda, 1938

The United States (US) population is 323 million (as of 2016), and health care provisions are important not only to the populace but also to politicians who seek election or re-election. Historically, US administrations have experienced tremendous difficulties when attempting to institute a national health insurance system. Obstacles included opposition from the American Medical Association, the insurance industry and pharma/medical business. \(^1\)\(^-\)\(^2\) The spectre of socialized medicine and ailing foreign health systems were typical cautionary tales utilised by opposition to and vested interests against a nationalised health service. \(^1\)\(^-\)\(^2\) President Lyndon B. Johnson first managed to introduce a modicum of basic national health insurance in 1965 with Medicare and Medicaid. \(^1\)\(^-\)\(^2\) These were crucial for certain population subgroups as uninsured patients are required to pay at point of care.

Medicare is a federal health insurance program that covers the over 65s, selected younger individuals with certain disabilities, and patients with end-stage renal disease requiring renal replacement therapy. As of 2015, Medicare beneficiaries totalled 55.3 million (age criteria: 46.3 million; disability criteria: 9 million). \(^3\)\(^-\)\(^4\) Medicaid is a state-administered federal program for low-income Americans who qualify by meeting certain federal income and asset standards, and by fitting into a specified eligibility. \(^3\)\(^-\)\(^4\)

Since 1965, further efforts to expand Medicaid coverage stalled until the enactment of President Obama’s Patient Protection and Affordable Care Act in 2010, so-called Obamacare. \(^5\) The Act’s major provisions were the expansion of Medicaid in order to insure more Americans, the establishment of state insurance exchanges, and the introduction of new federal subsidies to purchase private insurance for additional Americans. Moreover, Obamacare also strove to slow down the rate of growth of Medicare spending. Medicaid covered 50.9 million Americans in 2009 prior to the introduction of Obamacare and rose to 72.2 million in 2016. \(^4\)

Unfortunately, Obama’s administration failed to continue to enjoy its initially strong public support for health reform. The administration also failed to persuade many insured Americans that this reform would benefit them. For example, it was typically argued that the Act did not constitute true reform if it merely added tens of millions of new customers to private insurers’ rolls. It was also argued that this legislation, while greatly expanding access to health insurance, still left circa twenty-three million Americans without medical insurance coverage. Other arguments levied against Obamacare were that it lacked reliable cost control systems and did not permit most already insured Americans from joining the new insurance exchanges. Obamacare was nicely summarised thus:

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**Editorial**

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The legislation does not so much create a new health system as fill in gaps in the existing system, since the first principle of feasible reform was to build on current arrangements. It is a product of our fragmented political institutions, which compel compromise, and our fragmented health care system, which limits reformers’ options to move away from the status quo.\(^5\)

President Donald Trump, who succeeded President Obama in 2016, vowed to repeal Obamacare, citing all of its perceived disadvantages. This stance comprises part of a Republican trend to reduce or eliminate government spending on health and social services. However, it is estimated that the repeal of the Patient Protection and Affordable Care Act would leave 32 million Americans bereft of medical insurance, overnight. Moreover, there is no extant plan to replace this legislation with any equivalent or substitute.\(^6\)

Malta’s National Healthcare is modelled on the United Kingdom’s National Health Service, with free service at point-of-care against a contribution that is directly deducted from salaries, or as a monthly contribution for those who are self-employed. These two ways of contributing towards health and social services comprise a form of state-organised insurance. While arguably not perfect, in Malta, emergency and essential healthcare is available to all without additional payments. Poverty is thus not a barrier to healthcare access.

With regard to actual costs, Malta spends USD 307 per capita per annum on total health expenditure, thirty times less than the United States at USD 9403 per capita per annum (2015 data).\(^7\) Compared to the far more expensive American system, Malta’s National Health System is cheaper, with a net that covers one and all, including our most vulnerable families and individuals.

**References**


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**Cover Picture:**

“Astral Birth”

*Acrylic on Stretched Canvas*

*By* Erika Zammit

Erika Zammit is a full time Artist specialising mainly in acrylic and oil paintings. She studied the Arts and History of Arts at Advanced level, and furthered her studies on her own. Her main specialisations are space paintings, portraits and figure drawings. At a young age she joined the NGO Special Rescue Group – St. Lazarus Corps as a volunteer. Growing up volunteering for this NGO was a major inspiration in her life, which lead her to study First Aid at Advanced level, and further become a lecturer in the subject. She is also a lecturer with the institute of Medical Emergency Education, and her subjects are Advanced First Aid, and basic life support.
Abstract
This review addresses what is new in functional and motility disorders in the lower gastrointestinal tract: biomarkers and actionable biomarkers in irritable bowel syndrome (IBS), dietary and pharmacological treatment of abdominal pain in IBS, how to screen for rectal evacuation disorders in chronic constipation, hypotheses on the etiology of infantile colic, and lessons learned from the appraisal of an esoteric colonic motor disorder, that is, megacolon in association with multiple endocrine neoplasia type 2B. Understanding the mechanisms has moved these from idiopathic or cryptogenic disorders to organic diseases and has changed the attitude of health care providers to empathize with the suffering and legitimate pleas of millions of patients for effective therapies.

Key words
IBS, rectal evacuation disorder, chronic, diarrhea, constipation, megacolon

Introduction
Irritable bowel syndrome (IBS) is generally diagnosed based on symptoms of persistent abdominal pain that is associated with diarrhea (IBS-D), constipation (IBS-C), or both (IBS-M). The diagnosis should rely on the clinical history so that invasive and expensive testing can be avoided. However, the diagnosis of IBS may not be easy and may involve multiple clinic and emergency room visits, extensive investigations including blood and fecal tests, and multiple radiographic and endoscopic studies to exclude inflammatory bowel diseases (IBD), celiac disease, and gastrointestinal infections. There have been significant advances in the understanding of motility and functional lower gastrointestinal disorders that augur well for optimizing management of patients with these conditions.

There is considerable evidence of abnormal peripheral mechanisms in IBS. Several biomarkers have been proposed in IBS [Figure 1], including fecal, blood, mucosal, microbial, radiological (including brain imaging), and genetic markers. IBS biomarkers’ clinical utility greatly depends on our understanding of their functions in normal physiology and in the pathophysiology of IBS. A clinically useful biomarker needs to be safe, easy to measure, cost effective and actionable. The term “actionable” biomarker reflects the fact that the biomarker is helpful for the subclassification of diseases and directly impacts the selection of therapy. Validated
biomarkers may, in the future, potentially replace symptom-based criteria for IBS and aid in accurately identifying subgroups of patients beyond the symptom-based classifications, that is, bowel dysfunction and the presence or absence of significant pain.

Figure 1: Biomarkers in IBS. Reproduced with permission from ref. 63

Antibody panels
Antibodies to cytolethal distending toxin B (cdtB) (a toxin produced by C. jejuni) and Viniculin (component of adherens junction proteins) have been proposed for differentiating IBS-D from IBD and health. However, anti-CdtB antibody was also elevated in patients with celiac disease, an important diagnosis to be differentiated in patients with suspected IBS-D. This test is now commercially available as IBSchek.

A panel of 10 markers, consisting predominantly of antibodies or inhibitors to endogenous proteins or bacteria and neurotransmitters, was used to differentiate IBS from IBD, celiac disease and functional disorders. However, the sensitivity was only 50%. In addition, some of the biomarkers used in that analysis were not specific to IBS, and, thus, the test was not able to differentiate between the different subclasses of IBS. In another study, a different panel used 8 predominantly inflammatory biomarkers with a sensitivity of 88.1% and specificity of 86.5% to differentiate patients with IBS from healthy controls. Differentiation from other diseases mimicking IBS with this panel requires further study.

Further validation of these markers or panels in more diverse groups will help clarify their generalizability for application as diagnostic tests.

Bile acids
In clinical practice in the United States, quantifying fecal bile acids using a 48-hour stool collection is the gold standard test for bile acid
malabsorption. Other tests for detection of bile acid malabsorption (BAM) are used in other countries; these include $^{75}$Se-homocholic acid taurine (SeHCAT) retention test. Screening blood tests in development are fasting serum FGF-19, a regulator of hepatic bile acid synthesis which is low in BAM, and fasting serum 7α-hydroxy-4-cholesten-3-one (C4).

Several meta-analyses based on clinical studies have demonstrated that approximately 30% of patients with IBS-D has evidence of BAM. Deoxycholic acid (DCA) and chenodeoxycholic acid (CDCA) were lower in IBS-C patients compared to healthy controls.

Colesevelam, a bile acid sequestrant, sequestered intraluminal bile acids and increased stool consistency in IBS-D patients. In the future, ileal bile acid transporter inhibitors such as elobixibat may be available for patients with constipation.

**Calprotectin**

Calprotectin is a neutrophil-derived protein found in the cytosol of neutrophils; it acts as a biomarker for inflammation. Elevated fecal calprotectin helps differentiate patients with active inflammatory colitis such as IBD from those with microscopic colitis. Several studies in IBS patients have demonstrated similar fecal calprotectin levels compared to healthy controls and patients with IBD in deep remission.

A meta-analysis of 8 studies with 565 patients with IBD, 259 with IBS, and 238 healthy controls demonstrated that there was no level of fecal calprotectin that could completely exclude IBS.

Fecal calprotectin helps exclude IBD at a level <40 μg/g stool, but it is not a reliable biomarker for IBS. If IBD is excluded by imaging (e.g., colonoscopy), a high fecal calprotectin level may identify patients with immune activation as a component of the IBS mechanism.

**GI motility measurements**

Multiple tests are now available to evaluate gastrointestinal motility, including radiopaque marker studies, scintigraphy, and the wireless motility capsule. In a study of 287 patients with lower functional gastrointestinal disorders, approximately 30% had abnormal colonic transit by scintigraphy: delayed transit in 22.9% of patients with IBS-C and functional constipation, and accelerated transit in 33.3% of patients with IBS-D and functional diarrhea. Discordant results were rare: 4.5% of patients with IBS-D or functional diarrhea had delayed transit at 48 hours, and 4.2% of IBS-C or functional constipation patients had accelerated transit at 24 hours.

Abnormal colonic transit, measured by scintigraphy, was associated with symptoms including stool consistency, frequency of bowel movements, and ease of passage of stool. Colonic transit was an independent predictor of IBS compared to healthy volunteers, with well-established normal values (GC 24 of 1.3–4.4; GC48 1.9–5.0). Additionally, colonic transit with geometric center at 48 hours is an independent predictor in discriminating healthy individuals from IBS-C patients, and IBS-C patients from IBS-D patients, but it does not discriminate between slow transit due to colonic dysmotility and constipation due to rectal evacuation disorders.

**Psychological traits**

Psychological assessment has been used as a marker of illness in IBS. Psychological measures, such as the Hospital Anxiety and Depression scale, the Patient Health Questionnaire and the Perceived Stress Scale, have been added to enhance the ability of the IBS biomarker panels to differentiate IBS cases from healthy volunteers.

On the other hand, psychological markers used alone are likely not sufficient to identify bowel disturbances or their severity in IBS, but they may be more closely associated with the pain/discomfort in IBS.

**Actionable biomarkers in IBS**

Individually, symptom-based diagnostic criteria performed modestly in the prediction of IBS, and the diagnostic performance of symptom-based criteria is enhanced by additional history (e.g., nocturnal stools, somatization) and limited diagnostic tests (e.g., hemoglobin and C-reactive protein levels). A systematic review of biomarkers has appraised diverse markers. Overall, the most promising biomarkers with the greatest actionability are colonic transit and bile acid secretion, as they can be measured by several methods that are applicable in clinical practice. Additionally, there are specific efficacious therapies directed at reversing the pathophysiological mechanisms...
identified by those biomarkers.

Dietary and Pharmacological Treatment of Abdominal Pain in Irritable Bowel Syndrome

Abdominal pain remains the greatest unmet need in the treatment of IBS. A recent article appraised the available literature on dietary, probiotics and pharmacotherapy of pain in IBS, and a summary of efficacy is provided in Table 1. The main approaches to treatment remain antispasmodics and antidepressants, and it is hoped that advances in neurobiology of pain or further understanding of the microbiome might lead to novel approaches to therapy that remain experimental even for drugs that are used off-label, such as non-sedating anti-histamines and GABA-ergic agents.

Table 1: Efficacy of interventions on the relief of symptoms in IBS: Relative risk (RR) or odds ratio (OR) and confidence interval (CI) based on systematic reviews and meta-analyses. Reproduced with permission from ref. 29

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Parameter</th>
<th>RR or OR</th>
<th>Ref. #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bran, ispaghula and unspecified fiber</td>
<td>Abdominal pain</td>
<td>RR 0.87 (0.76-1.00)</td>
<td>49</td>
</tr>
<tr>
<td>Low FODMAP diet</td>
<td>Abdominal pain</td>
<td>OR 1.81 (1.13-2.88)</td>
<td>50</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Global improvement</td>
<td>SEM: -0.25 (-0.36, -0.14)</td>
<td>51</td>
</tr>
<tr>
<td>Probiotics: combination of E. coli + Enterococcus faecalis OR E. coli alone</td>
<td>Abdominal pain</td>
<td>RR 1.96 (1.14-3.36)</td>
<td>52,53</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Global improvement</td>
<td>OR 1.57 (1.22-2.01)</td>
<td>54</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Bloating</td>
<td>OR 1.55 (1.23-1.96)</td>
<td>54</td>
</tr>
<tr>
<td>Peppermint oil</td>
<td>Global improvement</td>
<td>RR 2.23 (1.78-2.81)</td>
<td>55</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant therapy</td>
<td>Global improvement</td>
<td>RR 0.66 (0.57-0.78)</td>
<td>56</td>
</tr>
<tr>
<td>Antidepressant therapy</td>
<td>Abdominal pain</td>
<td>RR 0.62 (0.43-0.88)</td>
<td>56</td>
</tr>
<tr>
<td>Antidepressant therapy</td>
<td>Global improvement</td>
<td>RR 0.67 (0.58-0.77)</td>
<td>57,58</td>
</tr>
<tr>
<td>Antidepressant therapy</td>
<td>Abdominal pain</td>
<td>RR 0.62 (0.43-0.88)</td>
<td>57,58</td>
</tr>
<tr>
<td>Drugs Targeting Specific Gastrointestinal Receptors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alosetron</td>
<td>Abdominal pain and discomfort</td>
<td>RR 1.30 (1.22-1.39)</td>
<td>59</td>
</tr>
<tr>
<td>Alosetron</td>
<td>Overall risk difference</td>
<td>0.13 (0.1-0.16)</td>
<td>59</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Adequate relief response</td>
<td>RR 4.7 (2.6-8.5)</td>
<td>61</td>
</tr>
<tr>
<td>Linaclotide</td>
<td>Adequate relief response</td>
<td>RR 1.95 (1.3-2.9)</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>RR 1.58 (1.02-2.46)</td>
<td>62</td>
</tr>
</tbody>
</table>
Chronic Diarrhea
Algorithm for evaluation of chronic diarrhea

Figure 2 shows a proposed algorithm for the diagnosis of chronic diarrhea.30 It is important to appraise the presence of rectal bleeding, features of malabsorption, or symptoms of IBS from the patients’ histories. If there are no rectal blood or features of malabsorption, a limited screen for organic disease may include hematology and chemical analyses, and tests to measure C-reactive protein, erythrocyte sedimentation rate, serum iron, folate, vitamin B12, tissue transglutaminase-IgA (to detect celiac disease), serum level of 7α-hydroxy-4-cholesten-3-one or fibroblast growth factor 19 (if available, to detect bile acid diarrhea), and examinations for excess fat or calprotectin in a random stool sample. In addition, colonoscopy and biopsy are usually performed according to recommendations for colorectal cancer screening, or in patients with intractable watery diarrhea to exclude microscopic colitis. American Gastroenterological Association guidelines specify the importance of excluding celiac disease, hyperthyroidism, IBS, and medication use (e.g. non-steroidal anti-inflammatory drugs, aspirin, proton-pump inhibitors, clozapine, and acarbose) when considering the possibility of microscopic colitis.31

Figure 2: Algorithm for management of chronic diarrhea. Patients undergo an initial evaluation based on different symptom presentations, leading to selection of patients for imaging, biopsy analysis, and limited screens for organic diseases. Reproduced with permission from ref. 30
The next steps in the management algorithm are guided by results of the initial screen for organic disease. The next steps include further specific tests when features indicate IBD or malabsorption. When results from all tests are normal and suggest chronic watery diarrhea typically without hypokalemia, opioid therapy should be tested (e.g. loperamide, 2–4 mg, as many as 4 times/day), with preprandial dosing for patients with prominent postprandial diarrhea. If the diarrhea persists, patients should be formally tested for bile acid malabsorption or given a trial of bile acid sequestrants if the tests for BAM are unavailable (e.g. 48h total fecal BA, or $^{75}$SeHCAT retention at 7 days; measurement of colonic transit will make it easier to select subsequent therapies. Tests for small intestinal bacterial overgrowth (SIBO- still best achieved by small bowel aspirates and culture) should be considered when there is evidence of malabsorption from the screening tests for organic disease, such as hypoalbuminemia or positive qualitative fecal fat.

**Management based on pathogenesis of chronic diarrhea**

The principles of management are accurate diagnosis and treatment of the specific factors that are causing the chronic diarrhea. Dehydration and severe electrolyte abnormalities are uncommon in patients with chronic watery diarrhea, but, when they occur, should be addressed with oral rehydration therapy.

Treating the factors that cause the disorder is more specific, such as with budesonide for microscopic colitis or a bile acid sequestrant for patients with diarrhea, and is certainly more intellectually satisfying. However, when that is not possible to direct treatment to a specific etiological mechanism, it is important to relieve symptoms with non-specific therapies that address the secretory and motor components of chronic diarrhea. Opioids are the mainstay of treatment and, when given in a scheduled regimen, are generally safe. However, a recent report found that high doses of loperamide can induce toxic cardiac arrhythmias and death.32

**Table 2: Summary and Dosages of Drugs Used in Treatment of Chronic Watery Diarrhea. Reproduced with permission from ref. 30**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Agent</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiates (μ-opiate receptor selective)</td>
<td>Diphenoxylate</td>
<td>2.5–5 mg, 4 times/day</td>
</tr>
<tr>
<td></td>
<td>Loperamide</td>
<td>2–4 mg, 4 times/day</td>
</tr>
<tr>
<td></td>
<td>Codeine</td>
<td>15–60 mg, 4 times/day</td>
</tr>
<tr>
<td></td>
<td>Opium tincture</td>
<td>2–20 drops, 4 times/day</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>2–20 mg, 4 times/day</td>
</tr>
<tr>
<td></td>
<td>Eluxadoline</td>
<td>100 mg twice daily (μ-opoid agonist and δ-opioid antagonist) for IBS-D</td>
</tr>
<tr>
<td>Adrenergic α2 receptor agonist</td>
<td>Clonidine</td>
<td>0.1–0.3 mg 3 times/day; Weekly patch</td>
</tr>
<tr>
<td>Somatostatin analogue</td>
<td>Octreotide</td>
<td>50–250 μg 3 times/day (subcutaneously)</td>
</tr>
<tr>
<td>Bile acid-binding resin</td>
<td>Cholestyramine</td>
<td>4 g daily or up to 4 times/day</td>
</tr>
<tr>
<td></td>
<td>Colestipol</td>
<td>4 g daily or up to 4 times/day</td>
</tr>
<tr>
<td></td>
<td>Colesevelam</td>
<td>1875 mg up to twice daily</td>
</tr>
<tr>
<td>Fiber supplements</td>
<td>Calcium polycarbophil</td>
<td>5–10 g daily</td>
</tr>
<tr>
<td></td>
<td>Psyllium</td>
<td>10–20 g daily</td>
</tr>
<tr>
<td>Soluble fiber</td>
<td>Pectin</td>
<td>2 capsules before meals</td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td>1000 mg twice or 3 times daily</td>
</tr>
<tr>
<td>Serotonin 5-HT3 receptor antagonists</td>
<td>Alosetron</td>
<td>0.5-1.0 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>2-8 mg twice daily</td>
</tr>
</tbody>
</table>
Deodorized tincture of opium and morphine are significantly more potent, but should not be prescribed for the indication of chronic watery diarrhea. Clonidine has been used to relieve the autonomic neuropathy associated with diabetic diarrhea, but may provide only limited benefit because of associated orthostatic hypotension. Use of the trans-dermal approach for clonidine may result in control of diarrhea without significant postural hypotension. Chronic intermittent antibiotics are the mainstay of treatment for well-proven SIBO. Several antibiotics have been shown to be equally effective. Although rifaximin is frequently prescribed, its use is limited by its high cost and regulatory approval for 3 courses, each of 2 weeks duration. Less expensive alternatives, such as metronidazole, doxycycline or ciprofloxacin, should therefore be considered. Agents that act intraluminally (fiber, pectin, and calcium) may be helpful in patients with small volume diarrheas. In some cases, a cocktail of agents with different mechanisms is required.

These and second-line approaches to use when first-line treatments fail are presented in Table 2.

### How to Screen for Rectal Evacuation Disorders in Chronic Constipation

Rectal evacuation disorders account for approximately one-third of patients presenting with constipation in gastroenterology practice. A recent population-based study showed that defecatory disorders are relatively common in the community, with the sex-adjusted incidence rate being 5-fold higher in women than in men. The most effective therapeutic approach to refractory constipation with rectal evacuation disorders is biofeedback therapy or pelvic floor retraining. To avoid laxative overuse in constipated patients with rectal evacuation disorders and to optimize treatment in these patients, an accurate diagnosis for rectal evacuation disorders is needed. Currently, the diagnosis for rectal evacuation disorders is based on anorectal manometry and evacuation tests (balloon, barium or MR defecography), which are not generally available in internal medicine or gastroenterology practices. Unfortunately, there is also considerable discordance among tests used for the diagnosis of rectal evacuation disorders, and also there is lack of standardization for the balloon expulsion test.

Therefore, in addition to careful clinical evaluation including digital rectal examination which is best for dyssynergic defecation, an easily accessible diagnostic tool with high specificity to select the patients with suspected rectal evacuation disorders is desirable prior to referral for specialized tests to confirm the diagnosis. There are several clinical pointers in the history and examination that can be used, to identify dyssynergic defecation. A carefully performed digital rectal examination by a highly experienced expert is a good screening test, with 75% sensitivity and 87% specificity. However, it is operator dependent and even gastroenterologists fail to perform the rectal examination for a variety of reasons. Therefore, there is need for a test that can corroborate the clinical impression and support referral for specialized anorectal testing. One test that is often performed to exclude other diseases in patients presenting with constipation is abdominal and pelvic computerized tomography (CT).

In 118 patients (102 females) who underwent CT abdomen and pelvis among >1500 patients with constipation evaluated by a single experienced gastroenterologist over 20 years, there were 63 with rectal evacuation disorders, 17 with slow transit constipation (STC), and 38 with normal transit constipation (NTC), based on the sum of the evidence from clinical findings and results of laboratory or radiological investigations. Using abdomen and pelvis CT, the rectal gas volume and maximal rectal gas transaxial area (MRGTA) were significantly greater in constipated patients with rectal evacuation disorders than in those without rectal evacuation disorders. Assessment of rectal gas area or volume on abdominal imaging may indicate rectal evacuation disorders in patients with constipation. At ~90% specificity for rectal evacuation disorders, the rectal gas volume of 20 or 30mL or MRGTA of 10cm² on CT have a positive predictive value of ~75%, and rectal area on scout film of >9cm² has a positive predictive value of ~69% [Figure 3].
Hypothese on the Etiology of Infantile Colic

Infantile colic is a syndrome characterized by recurrent irritability and inconsolable crying and screaming, accompanied by clenched fists, drawn-up legs, and a red face. It usually starts in the second or third week after birth, and peaks at 5 to 8 weeks of age. It generally stops spontaneously by 4 months of age. The prevalence is estimated to be between 5% and 28%. A recent review identified three hypotheses for the etiology of infantile colic. First, immaturity of hepatic synthesis, reduced intraluminal levels of bile acids, and impaired ileal absorption of bile acids in the neonate result in malabsorption of fat and other nutrients, with potential for secondary effects on colonic microbial flora. A second hypothesis proposes that the colonic microbial flora are abnormal and result in increased nutrient fermentation and reduced levels of dehydroxylated bile acids in the colon. Third, immaturity of the enteric nervous system (ENS) may lead to abnormal motor and sensory functions of the intestine and colon. Given the reversal of symptoms by 4 months of age, the concept that colic results from a dysmaturity of one of these digestive processes seems compelling.

Overall, the literature provides evidence for interaction among these three mechanisms. Understanding these potential mechanisms may lead to the introduction of diagnostic procedures that should enhance the selection or individualization of therapy for infantile colic.

Lessons from an Esoteric Motility Disorder

The most recognized gastrointestinal motility disorders presenting in neonates or infancy are congenital hypertrophic pyloric stenosis (which is easily managed by surgical pyloromyotomy and has undergone limited investigation of the genetic mechanisms) or Hirschsprung’s disease which is associated with several genetic abnormalities in Ret
kinase, endothelin B and its receptor, and SOX10 pathways.

On the other hand, multiple endocrine neoplasia type 2B (MEN2B) is an autosomal dominant syndrome caused by germline activating mutations of the RET proto-oncogene (typically at the M918T locus). It is associated in all patients with medullary thyroid cancer, and mucosal neuromas, and less frequently with phaeochromocytoma. Ganglioneuromas associated with megacolon are characterized by an increased number of ganglion cells and nerve fibers in all layers of the bowel wall.44 The ganglioneuromas can lead to loss of bowel tone, distension, segmental dilation and, ultimately, megacolon.

Megacolon is characterized on imaging studies by a permanently enlarged colon diameter which is greater than 6.5 cm at pelvic brim, greater than 8 cm in the ascending colon, or greater than 12 cm in the cecum.35 Infants with MEN2B frequently experience gastrointestinal symptoms,46 with constipation and intermittent diarrhea being the most frequently reported.47 Sixty percent of patients have prominent lips and 100% of patients have neurofibromas on their tongue, particularly the anterior two-thirds of the tongue. This physical finding should be sought, and plain abdominal radiograph should be conducted in patients presenting with abdominal pain, constipation, bloating and distension, as they may identify megacolon or rectal evacuation disorders (see above) which may be mistaken for chronic functional gastrointestinal disorders and yet could be eminently treatable by laparoscopic colectomy or retraining of the pelvic floor respectively. Indeed, 5 of 7 recently reported patients with megacolon associated with MEN2B underwent colectomy with excellent outcomes.48 Among these 7 patients with megacolon and MEN2B, 2 patients also had esophageal achalasia and 1 had a Zenker’s diverticulum; therefore, patients should be screened for esophageal dysmotility and treated according to the diagnosis.

Conclusion

There have been significant advances in the understanding of motility and functional lower gastrointestinal disorders that augur well for optimizing management of patients with these conditions. Perhaps, it is most important to recognize that understanding the mechanisms has moved these from idiopathic or cryptogenic disorders to organic diseases and has changed the attitude of health care providers to empathize with the suffering and legitimate pleas of millions of patients for effective therapies.

Grant support

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Acknowledgement

The author thanks Mrs. Cindy Stanislav for excellent secretarial assistance.

References


The acute use of oxygen therapy in adults

Richard Beasley, Darmiga Thayabaran, George Bardsley

Abstract

Over the last decade there has been an increasing realisation that oxygen should be considered a drug which is prescribed for specific indications to achieve a specific oxygen saturation range, and that the response needs to be monitored to guide ongoing therapy. This realisation has led to the development and promotion of guidelines which provide simple, practical and evidence-based recommendations for the acute use of oxygen in adults in clinical practice. In this commentary the Thoracic Society of Australia and New Zealand (TSANZ) oxygen guidelines are reviewed, and the key concepts and recommendations are presented.

Key words

Adult, Guideline; Hyperoxaemia; Hypoxaemia; Oxygen

Abbreviations

ABG: Arterial blood gas
BTS: British Thoracic Society
COPD: Chronic obstructive pulmonary disease
CPAP: Continuous positive airway pressure
ED: Emergency department
FiO₂: Fraction of inspired oxygen
HDU: High dependency unit
HFNC: High flow nasal cannulae
ICU: Intensive care unit
MDI: Metered-dose inhaler
NIV: Non-invasive ventilation
PaCO₂: Arterial partial pressure of carbon dioxide
PaO₂: Arterial partial pressure of oxygen
SaO₂: Arterial oxygen saturation measured by arterial blood gas
SpO₂: Arterial oxygen saturation measured by pulse oximetry
TSANZ: Thoracic Society of Australia and New Zealand

Oxygen is one of the most commonly administered medications in patients receiving emergency or hospital based care. It is probably also one of the most commonly misused medications, being frequently administered in high concentrations to patients who are not hypoxaemic and in whom its use is not indicated. This has led to calls for oxygen to be considered a medication that is prescribed and administered for specific indications, delivered through a specific device, at specific flow rates to achieve a documented target oxygen saturation range, with regular monitoring of the patient’s response.¹⁻³ It has also led to the development and publication of evidence-based guidelines by professional societies such as the British Thoracic Society (BTS)⁴⁻⁵ and the Thoracic Society of Australia and New Zealand (TSANZ).⁶

The key concept on which the guidelines have been based is that there are risks associated with both hypoxaemia and hyperoxaemia, leading to the recommendation that oxygen should be prescribed only if required, and if so, to within a target oxygen
saturation range. In the TSANZ guidelines this practice has been referred to with the colloquial term ‘swimming between the flags’. In this commentary the TSANZ oxygen guidelines for acute oxygen use in adults are reviewed. The use of long term domiciliary oxygen for patients with severe chronic respiratory disease is not addressed, and it is recommended that the BTS guidelines for home oxygen use in adults are reviewed.

Key Concepts

There are a number of key concepts on which the TSANZ guidelines are based. The first is that oxygen therapy is a treatment for hypoxaemia, not breathlessness. Oxygen therapy does not relieve the sensation of breathlessness in the absence of hypoxaemia. This has been shown in numerous clinical settings, with no clinical benefit of oxygen over room air for chronic obstructive pulmonary disease (COPD) patients with breathlessness who do not have severe hypoxaemia, or refractory breathlessness in the palliative setting. Furthermore, routine high concentration oxygen therapy does not improve outcomes compared with room air or titrated oxygen therapy to relieve hypoxaemia, in the treatment of acute coronary syndrome, and hyperbaric oxygen does not reduce mortality risk after stroke.

The second concept is that both hypoxaemia and hyperoxaemia may cause harm. Hypoxaemia is both a marker of the risk of a poor outcome due to the severity of the underlying disease(s) that has caused hypoxaemia, and an independent risk factor of poor outcome. While no absolute safe lower limit of hypoxaemia can be set, due to the differing clinical situations in which hypoxaemia can occur, oxygen therapy which achieves an arterial partial pressure of oxygen (PaO2) of at least 50 mmHg would prevent immediate life threatening risk from hypoxaemia.

Risk associated with high concentration oxygen can relate to both the high fraction of inspired oxygen (FiO2) administered and the level of hyperoxaemia resulting from the high FiO2. Potential risks include adverse respiratory (increased arterial partial pressure of carbon dioxide (PaCO2), absorption atelectasis and direct pulmonary toxicity), cardiovascular (increased systemic vascular resistance and blood pressure, reduced coronary artery blood flow, reduced cardiac output), cerebrovascular (reduced cerebral blood flow) effects, and increased reperfusion injury due to increased reactive oxygen species.

These competing risks at both ends of arterial oxygen tension have led to the ‘swimming between the flags’ concept of titrating oxygen therapy to within a specific target oxygen saturation range. It has also led to the proposal to realign the haemoglobin oxygen dissociation curve, to make the ‘slippery slope’ of oxygen desaturation less prominent, and accentuate the beneficial characteristics, enhancing both the pick-up of oxygen despite cardiovascular disease, and the drop off of oxygen to the tissues despite falling oxygen saturations (Figure 1). Through this different perspective of the haemoglobin oxygen dissociation curve, it might be possible to overcome the entrenched practice of doctors and other health professionals to administer high flow oxygen to breathless patients, regardless of whether hypoxaemia is present or not, for fear that the patient might get close to the ‘slippery slope’.

The third and related concept is that to achieve a target oxygen saturation range, pulse oximetry needs to be available in all clinical situations in which oxygen is used. However, clinicians need to be aware that the use of pulse oximetry to guide the titration of oxygen therapy is limited by its variable accuracy estimating arterial oxygen saturation (SaO2) in acutely ill patients, with oximetry measurements both over and under estimating SaO2, with wide limits of agreement.

The fourth concept is that the use of high concentration oxygen in a breathless patient in an attempt to protect against hypoxaemia in the event of a subsequent deterioration has the potential to delay the recognition of such a deterioration. This clinical approach may provide a false reassurance that the patient is stable. This is because there is unlikely to be any major change in vital signs or a marked decrease in SpO2 as assessed by pulse oximetry until a potentially life-threatening situation has developed. At this stage there is limited opportunity to further increase the oxygen therapy while medical review and an intervention such as transfer to a high dependency unit (HDU) or intensive care unit (ICU) is undertaken. This is illustrated by the hypothetical modelling of a patient deteriorating following presentation with pneumonia (Figure 2).
Figure 1: Oxygen haemoglobin dissociation curve (reproduced with permission from reference 3)

Left=traditional representation with “slippery slope” marked (SS)
Right=curve realigned to show the two key characteristics: (a) haemoglobin maintains high levels of saturation despite marked reductions in arterial oxygen tension, and (b) oxygen tension remains relatively preserved as oxyhaemoglobin saturation declines. These characteristics result in pick-up of oxygen by haemoglobin being maintained despite reduced oxygen tension, and delivery of oxygen to tissues being maintained despite progressively falling oxyhaemoglobin saturation.

Similarly, if a patient who requires a high FiO₂ to maintain adequate SpO₂ deteriorates there is limited capacity to increase FiO₂ to avoid life threatening hypoxaemia. For this reason, it is recommended that patients who need high FiO₂’s should receive senior clinician review and transfer to an area where there are appropriate numbers of competent staff able to provide more intensive monitoring and therapy.

Recommendations

Based on these concepts 10 key recommendations were made for the use of oxygen therapy, as follows:

1. Pulse oximetry should be available in all clinical situations in which oxygen is administered to patients. While acknowledging the variable accuracy of SpO₂ in critically ill patients, an SpO₂ of ≥92% is a practical lower threshold to rule out hypoxaemia, defined as an SaO₂ <90% or a PaO₂ <60mmHg (8 kPa). 

2. In the immediate assessment of an acutely unwell patient, oxygen saturations should be measured by oximetry, pending the availability of blood gas results if required. Arterial blood gas (ABG) measurement should be considered in the following situations:
   - Critically ill patients with cardiorespiratory or metabolic dysfunction
   - In patients with an SpO₂ <92% in whom hypoxaemia may be present
   - Deteriorating oxygen saturation requiring increased FiO₂
   - Patients at risk of hypercapnia (see below)
   - Breathless patients in whom a reliable oximetry signal cannot be obtained.

Peripheral venous blood gas analysis is a less invasive test, however it does not provide an accurate estimate of PaCO₂ or PaO₂. It does, however, provide rapid clinically important information to assess acutely unwell patients, including pH, lactate, glucose, haemoglobin, sodium and potassium. In addition it provides a venous partial pressure of carbon dioxide which if less than <40 mmHg, effectively rules out hypercapnia.
documented in the patient records and the drug chart. The main requirement for an oxygen prescription is documentation of the target SpO\textsubscript{2} range.

4. An SpO\textsubscript{2} target of 88% to 92% is recommended in exacerbations of COPD and other conditions associated with chronic respiratory failure (such as obesity hypoventilation syndrome, bronchiectasis, cystic fibrosis, neuromuscular disease and chest wall deformities such as severe kyphoscoliosis). Where there is diagnostic uncertainty as to whether COPD is the primary cause of the exacerbation, it may be preferable to titrate oxygen therapy to the 88-92% SpO\textsubscript{2} target range.

5. In the presence of hypoxaemia in other acute medical conditions not associated with chronic respiratory failure, oxygen should be administered to achieve a target SpO\textsubscript{2} range of 92% to 96%. There is considerable rationale for this range which is lower than the 94 to 98% range recommended in the BTS guidelines.

6. Patients who need an estimated FiO\textsubscript{2} of >0.40 (such as >6 litres per minute via a simple face mask) to maintain an adequate SpO\textsubscript{2} should receive senior clinician review and may require transfer to a facility such as an HDU, where there are appropriate numbers of competent staff able to provide more intensive monitoring and therapy.

7. Patients who need an estimated FiO\textsubscript{2} of >0.50 (such as >8 litres per minute via a simple face mask) to maintain an adequate SpO\textsubscript{2} should receive ICU review and most will require ICU transfer.

8. For most patients standard nasal cannulae are the preferred method of oxygen delivery, with the flow rate varied to achieve the target oxygen saturation. The main advantages of nasal cannulae are the ability to give nebulised bronchodilator at the same time as oxygen administration, and to prescribe oxygen at variable flows to achieve a target saturation range rather than a fixed FiO\textsubscript{2}.

Humidified high flow nasal cannulae (HFNC) are an alternative to standard low flow nasal cannulae or high flow masks for oxygen delivery. There are no established evidence-based recommendations to guide appropriate clinical use in adults, however currently some centres recommend HFNC only in the emergency department (ED), HDU or ICU.

9. In COPD and other conditions associated with chronic respiratory failure, if bronchodilator is required, the preferred methods of administration are via an air-driven nebuliser or via a metered dose inhaler (MDI) ± a spacer, with supplementary nasal oxygen continued as required. The reason for this is that the administration of bronchodilator via an oxygen-driven nebuliser has the potential to cause an increase in PaCO\textsubscript{2}.

10. In patients with hypercapnic respiratory failure, in whom an ABG measurement shows a pH <7.35 and PaCO\textsubscript{2} >45 mmHg, non-invasive ventilation (NIV) or invasive ventilation should be considered. COPD patients with a pH <7.26 managed with NIV require more intensive monitoring with a low threshold for intubation (if appropriate). In patients with severe cardiogenic pulmonary oedema continuous positive airway pressure (CPAP) should be considered. It is recommended that patients receiving ventilatory support are located in a ward area such as an HDU, ICU, a close observation unit or monitored bed unit, where there are adequate numbers of staff experienced in ventilatory support to provide an appropriate level of monitoring and titration of therapy.

A practical assessment and treatment algorithm was developed, encompassing these key concepts and recommendations, as displayed in Figure 3. It is suggested that the algorithm is modified as required to meet the needs of different health care settings.
Figure 2: Case example illustrating the potential for the ‘prophylactic’ administration of high flow oxygen to delay recognition of deteriorating cardiorespiratory function (reproduced with permission from reference 21)

The hypothetical case example of a patient with community acquired pneumonia presenting to medical care with a baseline SpO$_2$ of 88% (PaO$_2$ 58mmHg). The patient then deteriorates, with the intrapulmonary shunt increasing at a rate of 1% per 6 minutes. Two initial therapeutic approaches to oxygen therapy are considered, with an FiO$_2$ of (a) 0.3 and (b) 0.6.

In example (a), with an FiO$_2$ of 0.3, the time required for the PaO$_2$ to decrease from 80mmHg (SpO$_2$ 95%) to <60mmHg (SpO$_2$ <90%) is around 60 minutes. At this stage, with the same rate of increasing intrapulmonary shunt, an increase in FiO$_2$ from 0.3 to 0.6 will maintain the PaO$_2$ above 60mmHg for about a further 60 minutes.

In example (b), if the patient receives an FiO$_2$ of 0.6 it would take around 120 minutes for the PaO$_2$ to decrease to <60mmHg (SpO$_2$ <90%). At this stage, with the same rate of increasing intrapulmonary shunt, there will be a further deterioration in PaO$_2$ despite maintenance of the FiO$_2$ at 0.6.
Conflict of interest
Richard Beasley has received research funding from Fisher & Paykel Healthcare. Richard Beasley is a member of the TSANZ and BTS Adult Oxygen Guidelines Groups.

References

Asthma and chronic obstructive pulmonary disease are common diseases both characterised by airflow obstruction. Over recent decades the prevailing belief was that asthma and COPD were distinct diseases that can be easily distinguished and require different treatments. This stimulated basic scientific research aimed at obtaining a better understanding of both diseases, particularly COPD that had been neglected. The downside of this approach was that it resulted in the exclusion of patients from clinical trials that exhibited features of both diseases. However, it has been increasingly recognised that these patients are common in everyday clinical practice and that their exclusion from clinical trials meant that therapeutic decisions were not evidence based. The concept of the asthma COPD overlap syndrome is an attempt to develop diagnostic criteria for patients with features of both asthma and COPD. This is a necessary starting point from which to design studies to investigate the clinical features, aetiology, pathophysiology and prognosis of these patients, and ultimately determine treatment strategies. However, from the outset the concept of asthma COPD overlap syndrome has been controversial and has not gained universal acceptance.

In this review we will describe current definitions and concepts of the asthma COPD overlap syndrome and explore how our understanding of this syndrome may develop in the future.

Introduction
Asthma and chronic obstructive pulmonary disease (COPD) are chronic pulmonary diseases with similar clinical features and both are characterised by varying degrees of airflow obstruction. However, their aetiologies, pathology, progression and treatment responses differ markedly and guidelines produced by expert bodies have stressed the differences between the 2 diseases and the importance of diagnostic clarity. The Global Initiative for Asthma (GINA) defines asthma as ‘a heterogenous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.’ The Global Initiative for Obstructive Lung Disease (GOLD) defines COPD as ‘COPD is a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.’ These definitions are deliberately broad so as to be applicable in a wide range of countries and healthcare settings, including resource-poor environments where access to more sophisticated diagnostic tools may be limited. However, the disadvantage of such broad definitions is that patients may have clinical features that are included in the definitions of both asthma and COPD. For example some patients with a diagnosis of asthma may have ‘persistent airflow obstruction’ rather than ‘variable expiratory airflow limitation’ and patients with COPD can have symptoms that vary and variable airflow obstruction. Clinicians face
considerable diagnostic and therapeutic confusion when managing patients who have features of both asthma and COPD. Patients also face confusion when given different diagnostic labels of asthma or COPD by different clinicians. Therefore, experts have attempted to reach consensus regarding the diagnostic labels and clinical features that can be used to describe patients with features of both asthma and COPD. However, this approach remains controversial and the topic of fierce debate.

Asthma COPD overlap syndrome (ACOS)

Various terms have been used to describe patients with features of both asthma and COPD including asthma with chronic bronchitis, combined asthma and COPD, mixed asthma and COPD, asthma with irreversible airflow obstruction, COPD with asthmatic features and COPD with a reversible component. It was recognised that there are patients with features that ‘overlap’ both asthma and COPD as far back as 1995 in the COPD guidelines of the American Thoracic Society. However over the next two decades both clinical and basic science research focused on defining the unique clinical, pathological and inflammatory features of asthma and COPD, resulting in the prevailing view that they are two clearly distinct diseases. This was reflected in the design of clinical trials in which patients with overlapping features of both diseases were excluded and only patients with ‘pure’ asthma or COPD were included. However it became increasingly clear that such an approach resulted in only a minority of patients with asthma and COPD fulfilling the inclusion criteria for clinical trials. A large number of patients were excluded because they had clinical features of, or risk factors for, both asthma and COPD. A review published in 2009 by Gibson et al exploring this issue coined the term the ‘overlap syndrome of asthma and COPD’. This triggered a host of studies and expert reviews over the following years and in 2015 GINA and GOLD published a joint document proposing the term asthma COPD overlap syndrome (ACOS). However there has not been universal acceptance of the term or even the need for another diagnostic label in addition to asthma and COPD. Therefore debate continues how best to describe the range of patients with obstructive airway disease, particularly those that do not fit classical descriptions of asthma and COPD.

Definitions of ACOS

The GINA/GOLD document has described ACOS as ‘characterised by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD’ (8). The document emphasized that this is not a definition of a new disease but a ‘description for clinical use’, and that a specific definition cannot be developed until more is known about underlying mechanisms. It listed features that are individually characteristic of asthma and COPD and recommended that if a patient has features of both, this is suggestive of ACOS. So for example early age of onset, variable airflow obstruction, normal lung function between symptoms and symptoms that vary seasonally would favour asthma, whereas later age of onset, persistent airflow limitation and exposure to a risk factor such as tobacco smoke would favour COPD. While this is an easy to use pragmatic approach to the problem it has several drawbacks. Firstly the document did not define how many shared clinical features of asthma and COPD are required to diagnose ACOS, therefore this remains a subjective assessment on the part of the clinician. Secondly it is clear that patients with very different phenotypic (and probably mechanistic) features can be included under an umbrella of ACOS. For example a patient with lifelong asthma who has never smoked and has persistent symptoms and airflow obstruction would have features of both asthma and COPD. Equally a patient with a personal and family history of asthma and a smoking history with some variability in symptoms and airflow obstruction would tick different boxes but also fulfil criteria for ACOS.

Other expert societies have produced their own definitions of ACOS. In 2016 a global expert panel of specialists and generalists from North America, Western Europe and Asia proposed a set of diagnostic criteria consisting of 3 major criteria (1: Persistent airflow limitation (post-bronchodilator FEV1/FVC <0.70 or < lower limit of normal) in individuals 40 years of age or older; 2: ≥10 pack years of smoking or equivalent and 3: A documented history of asthma before 40 years of age or bronchodilator response ≥400 mL) and three minor criteria (1: Documented history of atopy or allergic rhinitis; 2: A bronchodilator response of ≥200 mL and 12% or greater on 2 different occasions and 3: A peripheral eosinophil count of 300/µL or greater). Patients who meet all 3 major
criteria and at least 1 minor criterion should be considered as having ACOS. Other national societies have also produced diagnostic criteria. Therefore it is clear that although there is broad agreement on what constitute the key clinical features of ACOS, as yet there is still no universally agreed definition. In the absence of such a definition epidemiological, mechanistic and therapeutic studies will continue to be difficult and plagued by the use of different definitions.

**Epidemiology**

As there is no agreed definition of ACOS, its prevalence in studies will depend on which definition is used. Most epidemiological studies have simply determined the proportion of patients with a physician diagnosis of both asthma and COPD and used this as a measure of the prevalence of ACOS. A review of general population studies from a number of different countries estimated the population prevalence of ACOS to range from 1.6% to 4.5%. In the USA the prevalence of patients with a physician diagnosis of both asthma and COPD has been reported as 2.7%. The prevalence of ACOS defined in this way appears to increase with age. In a survey of a random sample of the Italian population the prevalence of patients with a dual diagnosis was 1.6% in the 20-44-year age group, 2.1% in the 45-64-year age group and 4.5% in the 65-84-year age group. Among people aged > 40 years in five Latin American cities the prevalence of patients with a dual diagnosis was 1.7%.

Other studies have investigated the prevalence of dual diagnoses in patients with an existing diagnosis of asthma or COPD. A systematic review of five studies reported that the mean prevalence of ACOS defined in this way among patients with asthma or COPD was 20%. In a survey from the USA of 3,486 patients, 1,585 (45.4%) had asthma alone, 1,294 (37.1%) had COPD alone, and 607 (17.4%) had ACOS. In a literature review the prevalence of ACOS among patients with COPD ranged from 12.1% to 55.2%, and the prevalence of ACOS among asthma patients ranged from 13.3% to 61.0%. A meta-analysis of 27 studies identified COPD patients with a physician diagnosis of asthma or evidence of reversible airflow obstruction (≥ 12% and at least 200ml change in FEV1 from baseline, or ≥ 20% change in PEF or airway hyper-responsiveness). Using these criteria 27% of COPD patients were diagnosed with ACOS. Compared with patients with COPD only, ACOS subjects were younger, had a shorter smoking history and a higher BMI, but there were no differences between the groups in spirometry and the 6-minute walking distance. Among 1,488,613 adults in the USA with a diagnostic code of either COPD or asthma, 21.3% had a diagnosis of both asthma and COPD. Considering that these studies were carried out in diverse populations and used different definitions of asthma, COPD and ACOS, it is not surprising that the results are so varied. More definitive epidemiological data on the prevalence of ACOS will be impossible to obtain before a stringent, universally-agreed definition is available.

**Burden of disease**

Although the prevalence of ACOS continues to be debated, epidemiological studies have consistently demonstrated that patients with a dual diagnosis of asthma and COPD have worse outcomes compared with those with a single diagnosis. Studies from a number of different countries have reported that ACOS is associated with greater symptoms, worse lung function, more frequent exacerbations, hospitalisations, greater prevalence of anxiety and depression, impaired activity and more comorbidities. Some of these findings may relate to the increased diagnosis of ACOS with increasing age. However, it is clear that the burden of disease associated with a dual diagnosis of asthma and COPD is high and needs to be addressed.

**Therapeutic Implications**

Ascribing a diagnosis of asthma, COPD or ACOS to individual patients is not just of semantic or academic interest, but has a direct impact on treatment decisions. Clinical trials in asthma and COPD have utilised strict inclusion and exclusion criteria to ensure that a relatively ‘pure’ population is recruited. Patients with clinical features of both asthma and COPD have been excluded from clinical trials, resulting in a patient population that is not representative of the wider population seen in routine clinical practice. Halpin et al reported that the median eligibility of 36,893 patients with COPD for participation in 31 randomised controlled trials was only 23%. Other studies have reported...
eligibility rates ranging from 17% to 42%. The commonest reason for exclusion was a history of asthma, allergic conditions or atopy. In asthma even lower rates of suitability have been recorded with a lack of reversibility and a smoking history being common reasons for exclusion. These data suggest that the majority of ‘real life’ patients have features of, or risk factors for, both asthma and COPD, but are excluded from clinical trials. The systematic exclusion of these patients from clinical trials means that the effects of treatments in this population are unknown. In view of the high burden of symptoms, exacerbations and hospitalisations among these patients clinical trials are urgently needed that include these patients to determine the optimum treatment strategies.

Until relatively recently there appeared to be increasing convergence in treatments for asthma and COPD, with clinical trials reporting that inhaled corticosteroid (ICS)/long-acting β2-agonists (LABA) are beneficial in COPD, and long-acting muscarinic antagonists (LAMA) improve symptoms and lung function in asthma. Therefore such a convergence would suggest a diminished importance for distinguishing asthma, COPD and ACOS. However, a number of recent clinical findings have changed treatment recommendations in asthma and COPD, particularly regarding the role of ICS in COPD. There is evidence that ICS are inappropriately overprescribed in COPD, and current treatment guidelines are not being adhered to. This has become of growing concern as evidence has emerged of an increased risk of pneumonia associated with ICS use in COPD. At the same time as evidence has emerged of potential adverse effects of ICS in COPD, studies have reported that ICS withdrawal is safe in COPD, and that LABA/LAMA are equivalent to ICS/LABA in regards to exacerbation reduction. Together these emerging data have led to efforts to reduce inappropriate use of ICS in COPD. However, this could lead to underuse or withdrawal of ICS in patients with ACOS, with potential detrimental effects. For now this remains a hypothetical concern but it highlights the importance of including patients with features of both asthma and COPD in clinical trials and the danger in extrapolating the results of trials that recruit a highly select group of patients to the wider population seen in clinical practice.

Future directions

Although the concept of ACOS has helped to focus research attention on a previously neglected group of patients, concerns remain about adding another diagnostic label to an increasingly confusing landscape of airway diseases, phenotypes and endotypes. An alternative approach that has been proposed is to treat patients based on a personalised medicine approach and abandon disease labels. Under such an approach patients’ history and risk factors would be assessed through a comprehensive history and examination and the presence of airflow obstruction confirmed with spirometry. The focus would then be on identifying ‘treatable traits’ and comorbidities, rather than basing treatment on a diagnostic label. These traits may be pulmonary (e.g. eosinophilic airway inflammation, airflow obstruction, bacterial infection, chronic bronchitis), extra-pulmonary (e.g. obesity, gastro-oesophageal reflux disease, upper airway disease) or behavioural/lifestyle factors (e.g. smoking, allergen exposure, air pollution). There is evidence that current diagnostic labels are inadequate in describing and distinguishing inflammatory patterns in patients with chronic airway disease and therefore the alternative approach has the advantages of recognising the clinical and biological complexity of chronic airway disease. It is hoped that this will then have the potential to offer an evidence-based and cost-effective approach to treatment.

However, a personalised medicine approach to airway disease also has potential disadvantages in that it is likely to require increased and more sophisticated diagnostic testing leading to increased costs. Such an approach may not be achievable in resource-poor settings or in primary care even in high-income countries where many such patients are currently managed. Such an approach also requires a better understanding of the biology of airway diseases to select the best biomarkers that can correctly phenotype diseases and predict treatment response. The recent failure of a biomarker-directed treatment to reduce exacerbations in asthma highlights the need for further research into understanding the biology of chronic airway diseases.

Conclusions

Many patients with chronic airflow limitation seen in routine clinical practice do not fit easily into...
neat definitions of asthma and COPD. As these patients were excluded from clinical trials the optimum treatment for these patients is not known. Characterisation of these patients as having asthma-COPD overlap syndrome has focussed attention on a previously neglected group of patients, but widespread acceptance of the term ACOS has been hampered by the inability to agree on a standardised definition. Debate continues as to whether a personalised medicine approach is superior to the use of diagnostic labels such as asthma, COPD and ACOS. It may be that currently ACOS is a useful concept but as our understanding of the biology and mechanisms of chronic airway diseases increases and robust biomarkers are discovered, then it may become either much better defined, or possibly, redundant.

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Abstract
Hypocalcemia is the most common complication following total thyroidectomy and could be due to direct injury or ischemic damage to parathyroid glands during surgery. Hypocalcemia adds significantly to hospital stay and cost of hospitalisation. While there are numerous proposed treatment algorithms for post-thyroidectomy hypocalcemia, there are no universally accepted standard guidelines or treatment algorithms available. We present a case of prolonged recalcitrant hypocalcemia post-total thyroidectomy, requiring hospitalisation for more than a month, to illustrate the practical problems we faced during management of this patient.

Keywords
Hypocalcemia, thyroidectomy, calcium, parathormone.

Introduction
While hypocalcemia is the most common documented complication post-total thyroidectomy, hypocalcemia requiring prolonged hospitalisation and intravenous (IV) calcium supplementation is relatively rare. Hypocalcemia occurs due to manipulation of parathyroids during surgery, devascularisation, venous engorgement or accidental removal.1 The incidence of temporary and permanent hypocalcemia is reported to be around 27% and 1% respectively.2 Since the risk of reactionary/secondary haemorrhage after 24 hours of thyroidectomy is very rare, symptomatic hypocalcemia is the main reason for prolonged hospitalisation post-thyroidectomy.3

The pre-operative factors associated with post-thyroidectomy hypocalcemia are still unclear and various scoring systems have been proposed to identify patients likely to develop post-operative hypocalcemia.4 Identification of at-risk patients allows earlier and more aggressive calcium correction regimens allowing for shorter hospital stays and invasive investigations in low-risk patients.

Feeling of ‘heat waves’ are a documented adverse effect of IV calcium gluconate, especially when given rapidly. We could not find any literature linking either severe thrombophlebitis or high-grade fever with IV calcium injections. However, this is the second patient in our institute to develop high spiking fever coinciding with IV calcium injections.

Case report
A 39-year-old woman presented with thyromegaly and features suggestive of hyperthyroidism. She was worked up for the same
and diagnosed to have a multinodular goiter (MNG) with secondary thyrotoxicosis. Hyperthyroidism was controlled with carbimazole, thyroid status was optimised and patient was posted for total thyroidectomy. Intra-operatively, parathyroid glands were not identified and inferior thyroid artery branches were ligated and divided after crossing the recurrent laryngeal nerve (subcapsular vascular ligation). Intra-operative period was uneventful, patient was extubated and shifted to post-operative ward. 

In the evening following thyroidectomy, patient complained of tingling in the fingers. On examination, Trousseau’s sign was present (Figure).

**Figure 1: Bilateral carpal spasm**

Blood calcium levels were low, hence IV calcium gluconate bolus (10ml of 10% calcium gluconate in 100 ml 0.9% Saline) was given. Symptoms subsided but reappeared the next morning. Patient was started on thrice daily IV calcium boluses, however symptoms persisted and additional calcium boluses had to be given as needed. Patient also developed high spiking fever, for which she was worked up, and no evident source could be identified. Fever spikes coincided with IV calcium injections and patient developed pain and swelling around IV lines. A diagnosis of thrombophlebitis was made and IV lines were changed. Fever abated temporarily but reappeared. Patient developed episodes of symptomatic hypocalcemia whenever an attempt to taper calcium infusion was made. Hence treatment was altered: oral calcium reduced to 4g/day, oral calcitriol increased to 1.50 mcg (0.75mcg BD) daily, low dose hydrochlorothiazide (12.5 mg) added and salt restriction was advised. Calcium infusion was gradually tapered and stopped, and replaced with IV calcium boluses that were also gradually tapered and stopped. Patient did not have any further attacks of hypocalcemia or fever.

Patient was started on oral Vitamin D (60,000 IU once fortnightly), urine calcium and serum phosphate were assessed and calcitriol was reduced to 1.00 mcg/day and was discharged from the hospital after 46 days post-thyroidectomy.

Patient has since come for 5 follow-up visits. Serum calcium has stabilized and hence oral calcium supplementation was reduced. Calcitriol was gradually tapered and stopped. Oral Calcium was reduced to 60,000 IU monthly. Patient is currently doing well, with no constipation, fever or any symptoms suggestive of hypocalcemia.

**Discussion**

Severe hypocalcemia is one of the life-threatening complications post-thyroidectomy. The initial features of perioral numbness and tingling of fingers which often go unnoticed, can prove fatal due to cardiac arrest if prompt action is not taken at the appropriate moment.

Post-op hypocalcemia can be transient (lasting <12 months) or permanent, in which medical supplementation is required for more than 12 months. Post-thyroidectomy hypocalcemia may be asymptomatic, termed ‘lab hypocalcemia’ or symptomatic. Symptomatic hypocalcemia, severe hypocalcemia (corrected calcium <7.5mg/dl, <1.87
mmol/L) or hypocalcemia associated with ECG QT prolongation warrants hospitalisation and immediate IV calcium supplementation. Initial correction by bolus of 10 ml of 10% calcium gluconate in 50-100 ml 0.9% Saline/5% dextrose should be urgently administered in all cases of symptomatic hypocalcemia over 20 minutes, as more rapid infusion can cause lethal cardiac dysfunction. It is recommended that this be followed by IV calcium infusion regimen, as this bolus will only correct the calcium levels for 2-3 hours.

Accurate prediction of which patients will develop this complication is difficult, leading to unnecessary long hospitalisation to monitor for this rather rare complication. A meta-analysis published by Edafe et al identifies these factors as independent predictors of post-thyroidectomy hypocalcemia: (a) identification of <2 parathyroids during surgery; (b) reoperation for bleeding; (c) corrected calcium <7.5mg/dl or <1.87 mmol/L 24 hours post-surgery; (d) Graves’disease; (e) heavier thyroid specimens. An accurate risk stratification would allow for earlier and more aggressive institution of calcium correction regimens, possibly reducing hospital stay. This would also reduce unnecessary supplementation and investigations in the majority of patients who would not develop hypocalcemia. Albuja-Cruz et al have proposed a risk stratification protocol (Table 1). In this prospective study, the above-mentioned protocol was applied to 120 patients, demonstrating a significant reduction in calcium supplementation (P≤0.001) and hypocalcemic events (P=0.008). However, this protocol requires routine measurement of pre-and post-operative PTH levels, an expensive test that may not be justified given the low incidence of persistent, severe hypocalcemia. Another prospective study by Arer et al on 106 patients demonstrated that routine calcium supplementation can prevent early hypocalcemia post-thyroidectomy. A retrospective study by Maxwell et al confirms that routine supplementation of calcium and Vitamin D were associated with reduced cost and duration of hospitalisation with fewer episodes of hypocalcemia.

Recalcitrant hypocalcemia patients not responding to conventional doses of active vitamin D analogues (calcitriol or 1-alpha calcidol) and oral calcium, and requiring prolonged IV calcium are exceptionally rare. Treatment options for such patients include addition of thiazide diuretic and use of recombinant PTH. Thiazide diuretics also serve to offset the dose limiting side effect of Vitamin D and calcium supplementation: nephrocalcinosis due to increased renal calcium loss in the absence of the resorbptive effects of PTH on the renal tubules.

**Table 1: Proposed risk stratification protocol**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Recommended treatment</th>
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<tbody>
<tr>
<td><strong>High risk:</strong></td>
<td>Calcitriol 0.5 mcg BD + 6 g calcium daily</td>
</tr>
<tr>
<td>Post-op PTH &lt;10</td>
<td></td>
</tr>
<tr>
<td>and/or fall in PTH more than 60% from pre-op value</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate risk:</strong> Post-op PTH 10-19 and/or corrected calcium &lt;8</td>
<td>3 g calcium daily</td>
</tr>
<tr>
<td><strong>Low risk:</strong></td>
<td>Nil</td>
</tr>
<tr>
<td>PTH &gt;20 and/or corrected calcium &gt;8</td>
<td></td>
</tr>
</tbody>
</table>

Recombinant PTH (rPTH) is expensive, and there are no controlled trials demonstrating its effectiveness or safety in the setting of post-thyroidectomy hypocalcemia. However, it has a lower incidence of hypercalciuria, significantly reduces calcium and calcitriol requirement. A prospective phase 2 randomised trial by McLeod et al on 26 patients demonstrated that rPTH may prevent post-thyroidectomy hypocalcemia, shorten duration of hospitalisation and reduce the need for calcium and Vitamin D on discharge. The drug label carries a warning for osteosarcoma although this has only been observed in rats, at a dose much higher than what is generally used in humans. The cost of this injectable drug limits its use in clinical practice and it is only recommended for use in patients who cannot attain normocalcemia on oral calcium and Vitamin D supplements alone.

All patients receiving active vitamin D analogues and calcium supplementation should have regular monitoring of serum calcium and phosphate levels, until values stabilise. The lowest dose required to achieve a low-normal serum calcium while avoiding hyperphosphatemia should be administered. Shorter acting calcitriol should be replaced with longer acting vitamin D analogues.
such as cholecalciferol to simplify dosing. Also, urine calcium should be maintained less than 300 mg/24 hours to prevent nephrocalcinosis that can result in chronic kidney disease. This case highlights the significant morbidity and difficulty faced in managing a relatively simple complication. Accurate prediction and early institution of treatment could possibly reduce length of hospitalisation.

References
Case Report

A case of Hallermann-Streifff-François syndrome: an ophthalmological perspective

James Vassallo

Abstract

Hallermann-Streifff-François syndrome is a rare condition which offers multidisciplinary diagnostic and therapeutic challenges. The difficulty in dealing with these cases is compounded by the presentation at a very young age. The ophthalmologist has an important role in helping to establish a diagnosis and to recognize the need for early treatment to minimize amblyopia. This is a short report of the first documented local case which demonstrates many of the characteristic features of this syndrome and who has been followed up over three decades. A brief literature review is also presented.

Keywords

Hallermann syndrome, cataract, microphthalmia, amblyopia, Rubella

Introduction

Hallermann-Streifff-François syndrome (HSF) is a sporadic congenital condition characterised by multiple dysmorphic features, including ocular abnormalities. Prominent features include hypotrichosis, bird-like facies, brachycephaly with frontal bossing, dental anomalies, and proportionate dwarfism; mental retardation is uncommon. From the ophthalmic point of view, microphthalmia is consistent with the generalised small dimensions; the condition has been typically associated with congenital cataract, especially membranous cataract. There are numerous other ocular and systemic associations.

Case report

The medical notes of a 30-year-old female, who is a known case of Hallermann-Streifff-François syndrome, were reviewed. Her gestational history revealed that her mother had received the rubella vaccine at six months gestation.

Immediately after delivery she had multiple cyanotic attacks. Several dysmorphic features were noted early on: brachycephaly, facial hypoplasia, small nose and small nostrils with nasal congestion, low-set ears, and a small chest circumference (bell-shaped chest). Initial extensive investigations were normal, including karyotype, ECG, and echocardiogram.

Other general features that were documented over the following months included: frontal bossing markedly overhanging orbits, sunken eyes and down-slanting palpebral fissures, depressed broad nasal bridge with anteverted nostrils, small ear cartilages, small mouth, protruding tongue, early teeth eruption (noted at 20 days of age), micrognathia, prominent maxillae, long tapering fingers, pectus excavatum, sparse hair, hypotonia, psychomotor retardation, poor feeding and weight gain, with all growth parameters severely below the third centile. A clinical diagnosis of HSF was established at three months of age.

Her first ophthalmic review was requested at
five months. There were roving eye movements without fixation or following, aversion to bright light, microphthalmos, and leucocoria. An examination under anaesthesia was subsequently carried out and bilateral symmetrical mature cataracts and unilateral posterior synechiae were also noted. Nystagmus was apparent at six months.

Sequential bilateral lensectomy and anterior vitrectomy were performed at one year of age without significant intra-operative complications. Surgery was delayed due to recurrent respiratory tract infections. Other features that became subsequently apparent were a unilateral peaked pupil from vitreous incarceration, blue sclerae, and pale fundal reflexes due to fairly large areas of macular chorioretinal atrophy. She was fitted with aphakic glasses, initially +18.00DS OU, to which there was good compliance, and subsequently there was a great improvement in the response to her surroundings.

At five years of age she was started on timolol eyedrops unilaterally in view of an intra-ocular pressure (IOP) in the high twenties on the side of vitreous prolapse in the anterior chamber. The ocular media remained clear. At six years, she had a left medial rectus recession and lateral rectus resection for esotropia. Over the years IOP remained stable, perimetry shows asymmetrical stable central scotomas, and she developed unilateral lateral superior fornical conjunctival herniation. Figure 1 shows her current external features. The most recent appearance of the posterior poles with severe macular scarring is shown in Figure 2. Her latest refraction is: OD +14.00/-1.00x180 (6/20), OS +13.00DS (CFs to 6/120). The left eye is esotropic (Figure 3).

Discussion

This case describes the long-term follow-up of HSF. To our knowledge, this is the only documented case in Malta. HSF (HSS, oculomandibulodyscephaly with hypotrichosis, François dyscephalic syndrome, oculomandibulofacial syndrome) is rare with unknown prevalence and genetic basis. A search on PubMed reveals around 200 reported cases. It is postulated that mutations are sporadic, autosomal dominant with variable expressivity, with occasional chromosomal abnormalities.
François proposed seven diagnostic criteria: dyscephalia with bird-like face, dental abnormalities, proportionate dwarfism, hypotrichosis, cutaneous atrophy, microphthalmos, and congenital cataracts. However, as in this case, there are numerous other features that can occur and not all of the diagnostic criteria have to be present; the eyes may be spared in around 10% of cases. Ophthalmic associations reported are listed in table 1. The case outlined above also exhibited superior fornical conjunctival herniation which possibly represents herniation of orbital fat secondary to the microphthalmos.

This patient was exposed to the rubella vaccine during her gestation (end of second trimester). There is a previous report of a case of HSF whose mother was treated for rubella in the third month of pregnancy. Hence, it may be hypothesized that some of the ocular features seen in this case, such as the congenital cataracts and chorioretinal atrophy, may partly be due to the effect of the rubella vaccine.

In our case there was a delay between the diagnosis of HSF and ophthalmic referral, which shows that there could be a lack of awareness of the associated ocular features, and failure to recognize the importance of early treatment of any associated visually-significant cataracts. Cases of HSF are difficult to intubate and are prone to respiratory complications. This is due to the inherent difficulty presented by paediatric cases and particular anatomical features of HSF including glossoptosis and tracheomalacia. These issues can delay intervention which further reduces the visual prognosis in congenital cataracts and strabismus.

There was also a late increase in IOP, which was successfully controlled medically. The associated perimetric defects due to the optic disc colobomas may mask glaucomatous changes. Glaucoma is a rare feature of HSF. The elevation in intra-ocular pressure can be due to angle anomalies or inflammation. The latter may be
triggered by intra-ocular interventions such as cataract removal, hence post-operative anti-inflammatory treatment and follow-up are very important.

In summary, a case of Hallermann-Streiff-François syndrome with long follow-up has been presented, with particular attention to the ophthalmic findings. These cases are diagnosed clinically, with bilateral microphthalmos and cataracts being primary initial clues. These cases require multidisciplinary treatment and multiple procedures. Early management of associated cataracts can limit the subsequent amblyopia, with patients generally being left aphakic. New issues can emerge over time and regular re-assessment is warranted.

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