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CANADIAN PRIMARY CARE TODAY

Clinical Insights, Perspectives, and Disease Management

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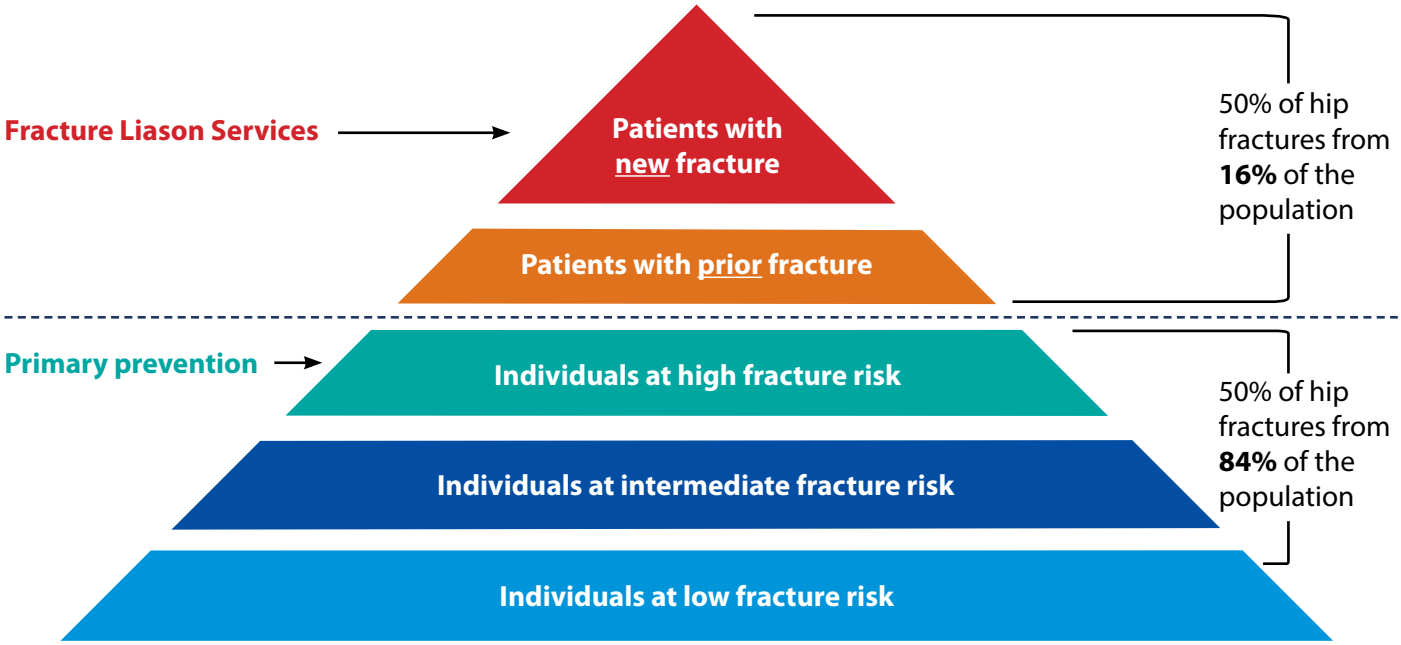
ESSENTIAL OSTEOPOROSIS MANAGEMENT FOR THE PRIMARY CARE PROVIDER

Introduction

Most individuals will experience deterioration in bone with advancing age, with consequent increases in fragility fractures. In addition, falls become more frequent with age, further increasing fracture risk. It is important to note that osteoporotic fractures impair quality of life and lead to increased dependency to a much greater degree in elderly individuals. Because of menopause-related declines in estrogen, women have greater bone loss and increases in fragility fracture compared to men. Our increased understanding of osteoporosis, its epidemiology, fracture risk, and expanding management options provide excellent opportunities for clinicians to benefit patients and maintain quality of life in aging individuals.

Osteoporosis Care Gap

Osteoporosis is a chronic disorder with great human costs as well as societal expense. There are many opportunities to intervene and benefit individuals at risk of fracture, both with primary prevention (prior to fragility fracture) and secondary prevention (subsequent to fragility fracture). This is analogous to managing patients at risk of myocardial infarction. Cholesterol, blood pressure, diabetes mellitus, and other risk factors are predictive of cardiovascular events, but most predictive is a prior myocardial infarction. In osteoporosis care, bone density and tools such as FRAX to estimate 10-year fracture risk can be helpful predictors, but are not nearly as potent as recognizing patients who have already had osteoporotic fragility fracture. These individuals are at the highest risk of future fracture events. By evaluating patients subsequent to acute osteoporotic fracture or with prior diagnosed osteoporotic fracture, one could screen only 16% of the postmenopausal female population to identify 50% of individuals who may proceed to hip fracture (**Figure 1**). These prevalent fracture patients, especially those having experienced a recent fragility fracture, can be easily identified since they have need of orthopedic, physiotherapy, cast clinic, rehabilitation medicine, and often in-patient care. Numerous cost economic models for identifying patients for secondary fracture prevention (after the initial osteoporotic fracture) have been published.[1] Fracture Liaison Services (FLS)



The majority of post-menopausal women (84%) have not suffered a fragility fracture. Strategies to case-find new and prior fracture patients could identify up to **50% of all potential hip fracture cases from 16% of the population.**

Figure 1. Fracture liaison services' role in identifying patients at high risk of fragility fracture.[14] Curr Med Res Opin 2005;21:4:475-482 Brankin E et al.; *courtesy of David Kendler, MD*

employ healthcare professionals to identify fragility fracture patients from facilities including the emergency room, cast clinics, and hospital wards and direct them to appropriate evaluation and osteoporosis management. Such FLS programs are present in many but not all care facilities.

Role of The Family Care Provider in Addressing The Osteoporosis Care Gap

Primary care providers can be instrumental in discussing osteoporosis and fracture risk with their patients. Frequently patients will attribute fractures to the force of their fall rather than bone strength. Obviously, all fractures are in part related to the force of the fall and in part related to the strength of the bone. Although not all fractures are fragility fractures, in individuals over age 65 the vast majority of fractures are related to bone strength and are amenable to osteoporosis therapies. Primary care providers can help counsel patients after fragility fracture by utilizing the three talking points for post-fracture patients identified by the American Society for Bone and Mineral Research (ASBMR) **(Table 1)**. Family doctors can screen their patients for fracture risk beginning around age 50. Those with clinical risk factors may be appropriate to proceed to bone density testing and 10-year fracture risk determination by FRAX. FRAX integrates clinical risk factors with BMD, providing greater acumen in identifying patients in need of osteoporosis pharmacotherapy and also helping primary care providers explain to their patients

• Their broken bone likely means they have osteoporosis and are at high risk for breaking additional bones, especially over the subsequent 1-2 years
• Breaking bones means they may, for example, have to use a walker, cane or wheelchair, or relocate from their home to a residential facility and will be at higher risk for dying prematurely
• Most importantly, there are actions they can take to reduce their risk

Table 1. Primary care communication to patients after hip or vertebral fracture: Three simple messages to patients and their family/caregivers throughout their fracture care.[15]; *courtesy of David Kendler, MD*

why treatment may or may not be required. If patients are identified, screening for the secondary cause of bone loss is important. In addition to clinical history and physical examination, chemistries may be helpful **(Table 2)**. Lateral thoracic and lumbar spine radiographs with instructions for the radiologist to identify vertebral fractures may be helpful with stratification of fracture risk. Family doctors may also provide specialist referrals for those patients at very high

risk, with treatment contraindications, or with complicated secondary osteoporosis etiologies.

Diet and Lifestyle Advise For Patients at Risk of Fracture

Dietary calcium sources may be deficient in elderly individuals, requiring dietary counselling or calcium supplementation. If an individual is able to achieve 3 or 4 dairy servings or the equivalent per day, a calcium supplement is not required. However, if dietary calcium is limited to 2 servings, a 500 mg calcium supplement taken with a meal will help to achieve the 1200 mg elemental calcium daily which is recommended. Vitamin D is synthesized in the skin after sunlight exposure, however older individuals have less effective synthesis of vitamin D, and there are few dietary sources of vitamin D. Although vitamin D stores can be assayed by serum 25 hydroxy vitamin D testing, this is expensive and not recommended for screening. A dosage of 1000 to 2000 IU vitamin D3 by daily supplement should achieve vitamin D sufficiency in the majority of elderly individuals. The Institute of Medicine tolerable upper limit of vitamin D supplementation is 4000 IU daily.[2] Many patients ask about other minerals and supplements. Although marketing messages are common, there is no evidence of the need for routine supplementation of magnesium, vitamin K2, boron, collagen, or complex calcium supplements. Patients should understand that magnesium is a laxative and may be helpful to relieve constipation, but if taken in excess may result in diarrhea. Especially for older patients with high fracture risk, and an exercise prescription is required. Exercise can offset muscle loss, weakness, frailty, and fall risk. There are many resources identifying interventions such as gait and balance training, to reduce the risk of fall https://osteoporosis.ca/exercise-recommendations/.[3]

Serum Chemistries: Calcium, Phosphate, Alkaline Phosphatase, Albumin, creatinine, eGFR, Complete blood count, 25-OH vitamin D, 24-hour urine calcium, Thyroid function tests (TSH, Free T4), Celiac antibodies, Serum/Urine Protein Electrophoresis.
Laboratory Tests in Specific Cases: Parathyroid hormone (PTH), Ionized Calcium, Total, Free, Bioavailable Testosterone, estradiol, LH, FSH, Prolactin, CTX (marker of bone resorption), Magnesium, Tryptase, urinary free cortisol.
X-rays of thoracic and lumbar spine
Screening tests for secondary causes of bone loss and bone fragility

Table 2. Blood chemistries for screening for the secondary cause of bone loss; *courtesy of David Kendler, MD*

Stratifying Patients By Degree of Fracture Risk: Very High Fracture Risk Patients

As a variety of osteoporosis therapies with varying actions and significantly different costs are available, the clinician must identify patients at very high fracture risk and target them to our most potent and rapidly-acting treatments. Patients at high risk of fracture may be effectively managed initially with less potent treatments. Patients with a recent osteoporotic fracture are at the highest risk of subsequent fracture and this risk is greatest in the first 1 to 2 years after their index fracture event. Data from Sweden, Iceland, USA, and Canada all support the concept of "imminent fracture risk" with very high fragility fracture risk early after index fracture.[4-7] Fragility fracture identifies patients at imminent risk for subsequent fracture. A recent update to FRAX, "FRAXplus®" allows integration of index fracture site and recency as well as other clinical risk factors not included in FRAX.[8] In order to aid the clinician in stratifying patients, recent guidelines, such as those published by the American Association of Clinical Endocrinologists (AACE) have proposed clinical criteria for very high fracture risk **(Figure 2, Table 3)**.[9]

Oral Antiresorptive Agents

Available oral antiresorbers include estrogen, selective estrogen receptor modulators (SERMs) (raloxifene, bazodoxifene), and oral bisphosphonates (alendronate, risedronate). Oral antiresorptive therapies preserve the existing bone architecture usually with transient modest increases in bone density plateauing after 2 or 3 years of therapy. Oral or transdermal estrogen may be an appropriate antiresorber for the short-term management of symptomatic early postmenopausal women. SERMs may provide reduction in breast cancer risk as well as reduction in vertebral fracture risk but may not provide adequate fracture protection in older individuals. Generic oral bisphosphonates are inexpensive and offer a unique opportunity for medication interruption after 3 to 5 years of treatment. The disadvantages of oral bisphosphonates include gastrointestinal intolerance, impaired absorption in many individuals, and demonstrated poor adherence to therapy in most real-world studies.

Parenteral Antiresorbers

Although a bisphosphonate, intravenous zoledronic acid infusion has greater potency and longer persistence of effect compared to oral bisphosphonate. Intravenous infusion assures absorption and adherence to treatment for at least the subsequent year. Longer drug holidays are therefore possible in many patients after intravenous zoledronic acid infusion. Acute phase reaction is a flu-like syndrome subsequent to intravenous zoledronic acid infusion, in about 10% of individuals, usually lasting a few days but which may be severe.

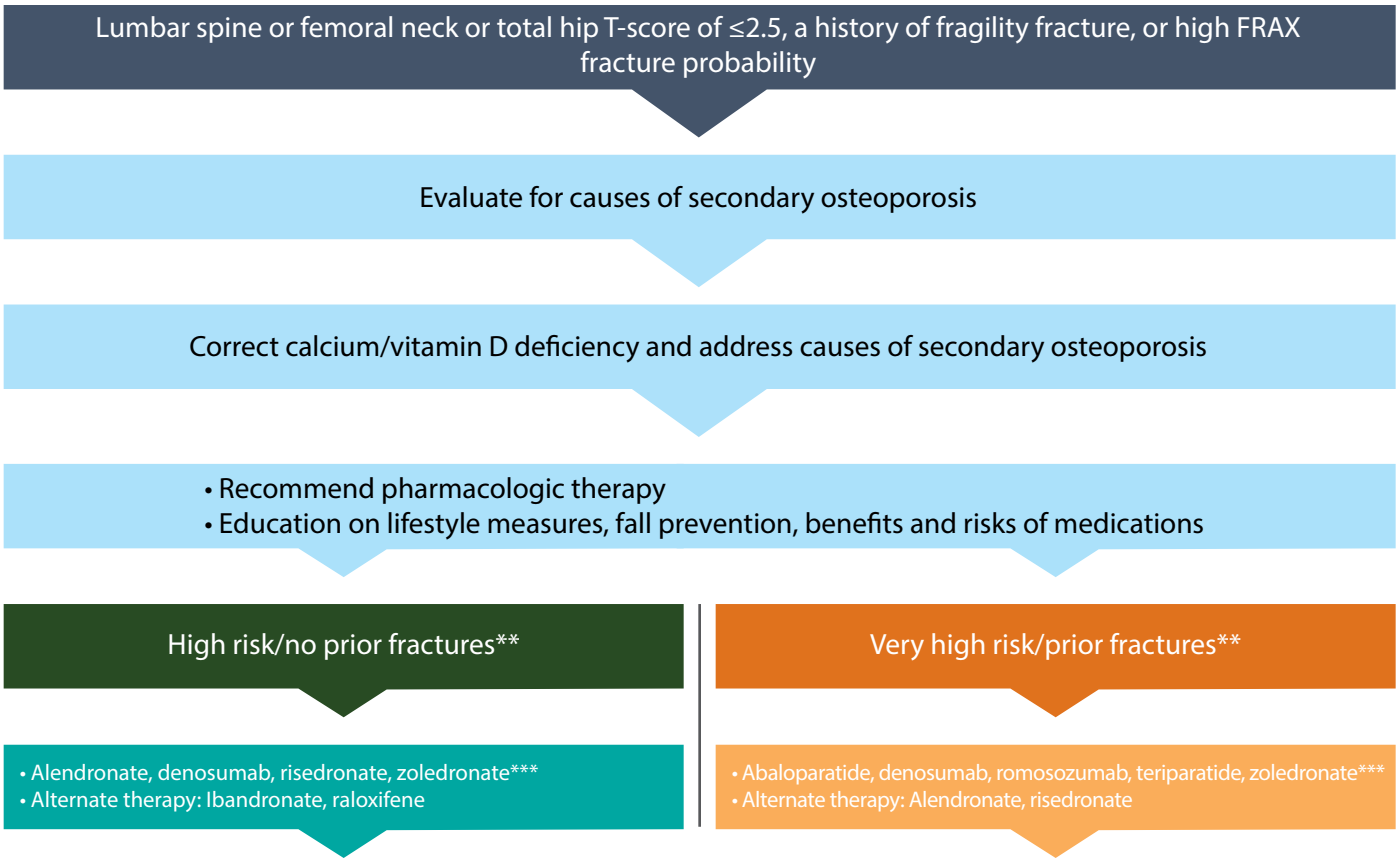


Figure 2. AACE clinical management algorithm for postmenopausal osteoporosis; *adapted from Camacho, PM et al., 2020*

Denosumab with six monthly subcutaneous injections provide RANK ligand monoclonal antibody, reducing number, function and survival of osteoclasts. This provides greater and ongoing improvements in BMD compared to bisphosphonates with greater anti-fracture efficacy. Like all other non-bisphosphonate treatments, if treatment is discontinued, antiresorptive effects reverse with consequent bone loss and the potential for fragility fractures in patients at risk. Therefore, patients discontinuing non-bisphosphonate antiresorptive therapy such as denosumab should be switched first to bisphosphonate, then after 3 to 5 years of bisphosphonate therapy, a subsequent bisphosphonate drug interruption may be possible.[10]

• Recent fracture (e.g., within the past 12 months)
• Fractures while on approved osteoporosis therapy
• Multiple fractures
• Fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids)
• Very low T-score (e.g., less than −3.0)
• High risk of falls or history of injurious falls
• Very high fracture probability by FRAX (e.g., major osteoporosis fracture >30%, hip fracture >4.5%)

Table 3. AACE criteria for determining very high fracture risk; adapted from Camacho, PM et al, 2020

Bone Anabolic Therapy

Bone anabolic therapy has a very different action on bone compared to antiresorptive therapy. With bone anabolic therapy, it is possible to reconstitute the trabecular and cortical bone architecture with much greater improvements in bone density, strength and demonstrated superior anti-fracture efficacy compared to antiresorbers. There are two different types of bone anabolic therapy: PTH receptor agonists therapies including teriparatide and abaloparatide both increase bone formation and bone resorption with the majority of new bone formation in the opened remodelling space. Romosozumab is a sclerostin monoclonal antibody with both antiresorptive and anabolic action on bone, forming most new bone on quiescent bone surfaces. Deciding between teriparatide and romosozumab is dependent in part on contraindications and in part on access and patient preference. Teriparatide requires daily

injections for two years at relatively high cost and with contraindication in patients with prior skeletal irradiation, Paget's disease, and skeletal malignancy. Romosozumab requires monthly injections for one year at relatively lower cost and with contraindication in patients with prior myocardial or cerebrovascular event.

Sequencing Osteoporosis Treatments/ Drug Holiday

A primary consideration regarding treatment sequence is that patients at very high fracture risk should be managed initially with bone anabolic therapy since initial antiresorptive therapy blunts subsequent bone anabolic therapy BMD response.[11] If a patient has inadequate response after oral antiresorptive therapy, they can progress to a parenteral antiresorber (zoledronic acid annual infusion, denosumab six monthly injections), or better still, to bone anabolic therapy (romosozumab or teriparatide). Although patients may express an interest in a "drug holiday," they should be made aware that this is available only to patients at low or moderate fracture risk after 3 to 5 years of bisphosphonate therapy. Clinicians are recommended to advise patients that bisphosphonates are like a persistent "coat of paint" on bone, therefore allowing moderate risk patients a two- or three-year bisphosphonate drug interruption with subsequent return to therapy.[12] It is important to explain that patients at high risk should not interrupt therapy (although they may switch to a parenteral antiresorber or bone anabolic therapy). Drug holiday is not recommended for other osteoporosis therapies including antiresorbers and bone anabolic therapy. Patients discontinuing non-bisphosphonate therapies should be switched to a bisphosphonate to prevent reversal of benefits to bone quality and anti-fracture efficacy.

Recent Osteoporosis Management Guidelines

A number of osteoporosis management guidelines have recently been developed by a variety of organizations representing physicians managing osteoporosis. Most guidelines do not have strict first- and second-line recommendations for therapy but rather, they encourage tailoring treatment to individual patient need. Although there are differences, most guidelines identify a "very high risk" population distinct from high-risk patients. This is helpful as it encourages physicians to stratify patients and direct the most potent and rapidly-acting agents to those at the highest risk of fracture. All guidelines encourage the recognition of prior fragility fracture as a prime risk factor for future fragility fracture. Most guidelines recognize that the lack of identification of fragility fracture patients is one of the leading causes of the osteoporosis care gap which must be addressed. All guidelines attempt to put in perspective the risks of osteonecrosis of the jaw and atypical fracture against the documented and substantial improvements in bone strength afforded by osteoporosis therapies.[13] Reevaluation of patients after 3 to 5 years of bisphosphonate therapy with potential drug holiday or switching to denosumab or anabolic therapy is recommended. Although there is no time limit to denosumab therapy, if discontinued, all guidelines recommend than an alternate antiresorber be initiated to prevent decline in BMD and return of fracture risk.

Conclusion

The past decade has seen significant advances in the understanding of osteoporosis epidemiology and fracture risk. In addition, we have new tools that are effective in reversing changes associated with menopause and maintaining normal bone turnover. Bone anabolic therapy should play a very important role in providing more effective fracture risk reduction for patients at very high fracture risk. Despite the advances made, there remains a significant care gap with many patients at high or very high fracture risk not being identified, not being evaluated, and not being afforded the opportunity to initiate treatment which would have significant benefits to their future independence and quality of life.

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ASCVD=atherosclerotic cardiovascular disease; CI=cardiac index; LDL-C=low-density lipoprotein cholesterol; Q2W=every 2 weeks; QM=monthly

* LAPLACE-2 study design: Phase 3, 12-week, randomized, double-blind, placebo- and ezetimibe-controlled trial (N=1,896) in patients with primary hyperlipidemia (including 526 who had ASCVD) on maximum dose statin therapy. Patients were initially randomized to an open-label specific statin regimen for a 4-week lipid-stabilization period followed by random assignment to Repatha® 140 mg Q2W, Repatha® 420 mg QM or placebo for 12 weeks as add-on to daily statin therapy. Baseline LDL-C was 2.8 mmol/L, measured after the lipid stabilization period and before administration of first dose of Repatha®. Primary endpoint: Mean % change from baseline in LDL-C at week 12. Select secondary endpoint: Proportion of patients achieving LDL-C <1.8 mmol/L.[1,2]

References: 1. Repatha® (evolocumab injection) Product Monograph. Amgen Canada Inc., September 27, 2023. **2.** Robinson JG, *et al.* Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: The LAPLACE-2 randomized clinical trial. *JAMA* 2014;311(18):1870-82. **3.** Amgen Data on File.

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THE LATEST UPDATES IN OBESITY MANAGEMENT IN PRIMARY CARE

Obesity Clinical Practice Guidelines – What's New

The Canadian Obesity Clinical Practice Guidelines, published in 2020, have significantly shifted the dialogue around obesity management. These guidelines place substantial emphasis on patient-centered care, reducing stigma and bias, and recognizing obesity as a chronic disease, and have set a new global standard for obesity management. Most recently, Ireland and Chile have adapted these guidelines in their own countries.

The approach to obesity treatment has evolved from a linear model of lifestyle modification followed by medication and then considering bariatric surgery, to a three-pillar strategy.[1] This strategy is underpinned by medical nutritional therapy and physical activity which, although crucial for overall health, are not effective standalone tools for obesity and often fall short of success with long-term weight reduction.

Obesity is defined as a chronic, progressive disease caused by dysfunctional adipose tissue that increases hunger hormones and lowers metabolic rate (thermogenic adaptation) in response to weight loss. This biological defense mechanism explains why diet and exercise alone are often insufficient for managing this chronic condition.[2] This is also the reason why we have moved away from relying solely on the BMI calculation to diagnose obesity.

Obesity is now diagnosed using multiple characteristics including BMI, waist circumference and, most importantly, health consequences from excess adiposity. The three pillars of treatment for obesity include behavioural/psychological interventions, pharmacotherapy, and bariatric surgery **(Figure 1)**. These treatment modalities directly address the consequences of dysfunctional adipose tissue and are considered the only true long-term treatments for obesity.

Since its initial publication, the guidelines have updated the obesity pharmacotherapy chapter to include the newest addition of medication options, specifically, adding Wegovy (semaglutide 2.4 mg/week). There are now 4 Health Canada-approved medications for obesity: Orlistat, Saxenda (liraglutide 3 mg/day), Contrave (naltrexone/bupropion) and Wegovy (semaglutide 2.4mg/week) **(Table 1)**.

This update not only reviews the evidence for medication use and summarizes the efficacy of each agent but also introduces a new methodology for selecting the most appropriate pharmacotherapy option. The new recommendation suggests identifying the comorbidities related to obesity and choosing the pharmacotherapy agent based on this, amongst other patient and medication specific factors.

The GLP-1 RA class of medications, including liraglutide and semaglutide, has shown benefit in diabetes remission and HbA1c improvement, alongside Orlistat. Of medications used for the treatment of obesity, the GLP-1 RA class of medications is the only one beneficial for MASH (metabolic dysfunction-associated steatohepatitis) parameters. Liraglutide has been shown to improve the apnea-hypopnea index in those with obstructive sleep apnea, and Contrave has been shown to improve depression scores.[3] Both Contrave and Wegovy have shown an improvement in cravings. Wegovy is the only obesity medication that has demonstrated a cardiovascular mortality benefit in those with established cardiovascular disease, as seen in the SELECT trial.[5] Given these established improvements in adiposity-related health conditions, the choice of pharmacotherapy should take into consideration the desired health outcomes of the patient instead of focusing on weight loss alone.

The recommendation for choosing pharmacotherapy also emphasizes considering patient- specific factors such as cost/coverage, delivery method, medication interactions, contraindications, and efficacy, with a stronger focus on obesity-related health issues. There's also an important recommendation on prescribing medications as a long-term treatment for obesity, acknowledging that weight regain is likely once treatment is discontinued, regardless of treatment choice.[3] Prescribing medication also provides a valuable opportunity to discuss and educate patients about why obesity is considered a chronic disease, emphasizing the importance of medication compliance for long-term success.

Practical Tips For Obesity Management in Primary Care

Many primary care providers feel overwhelmed by the prospect of adding obesity treatment to their already extensive list of responsibilities. However, it's important to recognize that excess visceral fat increases a patient's risk of multiple health conditions, including metabolic conditions such as high blood pressure, fatty liver, high cholesterol, type 2 diabetes, heart disease, and cancer. It also increases the risk of mechanical health conditions such as sleep apnea and osteoarthritis, as well as mental health conditions including anxiety and depression. Addressing the main contributor of these conditions, obesity, is crucial for improved patient care and outcomes. Lastly, primary care professionals are best equipped to oversee chronic conditions such as obesity, due to established long-term therapeutic alliances with patients. Educating patients about the relationship between obesity and their mental and physical health in a truly

Medical Nutrition Therapy (MNT)

MNT is used in managing chronic diseases and focuses on nutrition assessment, diagnostics, therapy and counselling. MNT should:

a. be personalized and meet individual values, preferences, and treatment goals to promote longterm adherence
b. be administered by a registered dietitian to improve weight-related and health outcomes

Physical Activity

30-60 mins of aerobic activity on most days of the week, at moderate to vigorous intensity, can result in:

a. small amount of weight and fat loss
b. improvements in cardiometabolic parameters
c. weight maintenance after weight loss

Remember nutrition and physical activity recommendations are important for all Canadians regardless of body size or composition

The Three Pillars of Obesity Management that Support Nutrition and Activity

Psychological Intervention

a. Implement multicomponent behaviour modification
b. Manage sleep, time, and stress
c. Cognitive behavioural therapy and/or acceptance and commitment therapy should be provided for patients if appropriate

Pharmacological Therapy

a. liraglutide
b. naltrexone/bupropion *(in a combination tablet)*
c. orlistat

Criteria
BMI ≥30 kg/m² or
BMI 27 kg/m² with obesity (adiposity) related complications

Bariatric Surgery

Procedure should be decided by surgeon in discussion with the patient

a. Sleeve gastrectomy
b. Roux-en-Y gastric bypass
c. Biliopancreatic diversion with/ without duodenal switch

Criteria
BMI ≥40 kg/m² or
BMI ≥35-40 kg/m² with an obesity (adiposity) related complication or
BMI ≥30 kg/m² with poorly controlled type 2 diabetes

Treating the root causes of obesity is the foundation of obesity management - refer to the 4M framework - *mechanical, metabolic, mental and social milieu*

Figure 1. The Three Pillars of Obesity Management that Support Nutrition and Activity; *adapted from CMAJ Appendix 2, 2020 Clinical Practice Guidelines: 5As Framework for Obesity Management in Adults*

empathetic manner is essential. The initial step is to explain why obesity is a chronic disease and to illustrate how even a modest reduction of 5-10% in weight can significantly help in managing their other medical conditions. It is vital to manage expectations to help with long- term treatment success as most patients expect to lose more than 20-30% (on average) of their weight, which is unrealistic with most treatment outcomes. Your best weight is the one you reach by enjoying the healthiest lifestyle possible, and it's important to celebrate this achievement despite any difference from your expected ideal weight, as positive health outcomes can occur with any amount of weight loss.[6]

Almost every individual grappling with obesity has dealt with criticism, attempted various dieting approaches, and faced setbacks. As patients internalize these adverse events as personal failures, a phenomenon referred to as internalized bias, the effectiveness of treatment tends to diminish. By addressing the bias and stigma associated with obesity, reviewing the pathophysiology behind the body's defence of its highest weight, and explaining that safe and effective treatments are available, we can shift the conversation from frustration caused by unrealistic expectations to hope and optimism arising from more realistic goals.

To assist our patients, it is valuable to explore simple and practical ways to support those living with obesity. To begin a conversation, it is best to ask if they are open to discussing their weight. If they agree, express that even modest weight loss could improve their health and manage related conditions. Then inquire, "On a scale of 0 to 10, how confident are you that you can lose weight at this time?" If they answer '4', probe further with, "I'm curious, why did you answer with '4' and not '5'?" Their response will offer deep insights into their challenges and perceived barriers. Review the three pillars of treatment (behavioural therapy, medications, and surgery) and inquire about their preference(s) for safe and effective treatment.

Arrange a follow-up visit to discuss this further, just as with any other chronic conditions like type 2 diabetes or hypertension. This gradual, empathetic approach also facilitates practical lifestyle changes in an efficient way. Patients are appreciative and responsive as this level of empathy and understanding regarding their struggles

with obesity is unfortunately rare.

Quick Nutrition Tips: Is There a Best Diet?

There is no single best diet that suits everyone. The most effective diet is one that an individual can maintain long term. As we lose weight, our body naturally increases our appetite and control of eating becomes challenging which is why, in general, the recommendation is to avoid highly restrictive diets as they are rarely sustainable. Advising people to follow a diet that worked for you, a family member, or another patient is not beneficial, as individuals have different lifestyles and dietary preferences. A one-size-fits-all approach should be avoided.[4] Focusing on nutrition that keeps patients full and satisfied, with a healthy balance of macronutrients and a positive relationship with food should be emphasized.

Using motivational interviewing, as previously described, to identify the specific challenges a patient is facing, is helpful when establishing nutrition-based goals. Whether they are overeating due to lack of satiety, emotional eating, or cravings, it is important to work together on strategies to address challenges in a patient-centered way. Understanding high-risk times of the day or triggers for their cravings can significantly reduce their overall intake in a more sustainable manner. Remind them that while this approach may result in slower and possibly less weight loss initially, it reduces the likelihood of weight regain. If possible, referring patients to a dietitian or a certified bariatric educator can be helpful for creating individualized nutrition plans.

Managing Obesity in Patients Who Cannot Afford Obesity Medications

The cost of obesity medications presents a significant challenge. Currently, obesity medications are not covered by any provincial drug plan and are often not covered by private insurance. However, discussing the benefits of modest weight loss—including the need for fewer medications overall, increased energy, improved mental health, less joint pain, and better sleep—may persuade patients who are initially deterred by the cost to consider them. Many patients have spent significant amounts of money managing their weight through commercial programs, which can be redirected toward evidence-based treatments that have been shown to have long-term success.

Nevertheless, some individuals simply cannot afford these medications. In such cases, optimizing behaviours and overall health is still a valuable outcome. Inquire if they have access to a dietitian or other allied healthcare

Agent	Populations Showing Weight Loss Benefit in Clinical Trials*	Average Weight Loss at 1 year	Benefits in adiposity related health parameters	Cost	Provincial Coverage for Obesity Pharmacotherapy
Liraglutide 3 mg SC daily	Overweight and Obesity PreDM T2DM NASH OSA	-8.6% vs -2.6% placebo	Remission of PreDM A1C NASH parameters apnea-hypopnea index BP QoL	$$$$	None
Naltrexone-Bupropion 8/90 mg 2 tabs PO BID	Overweight and Obesity T2DM	-6.1% vs -1.3% placebo	A1C Depression scores Cravings QoL	$$$	None
Orlistat 120 mg PO tid	Overweight and Obesity PreDM T2DM	-10.2% vs -6.1% placebo	Remission of PreDM A1C	$$	None
Semaglutide 2.4 mg SC weekly	Overweight and Obesity PreDM T2DM NASH	14.9% vs -2.4% placebo	A1C NASH parameters BP Cravings QoL	TBD	None

Table 1. Medications Approved in Canada; *adapted from Pharmacotherapy in obesity management, Pedersen, SD et al., 2022*

*Clinical trials conducted in populations with overweight and obesity, and trials conducted in populates with overweight/obesity and specific comorbidities (PreDM, T2DM, MASH, OSA)

Abbreviation: preDM = prediabetes; **T2DM** = type 2 diabetes mellitus; **NASH** = nonalcoholic steatohepatitis**; OSA** = obstructive sleep apnea; **A1C** = hemoglobin A1C; **BP** = blood pressure; **QoL** = quality of life

support and consider the other two pillars of treatment (behavioural change and bariatric surgery). Importantly, review if they are taking weight gain promoting medications and consider alternatives where appropriate. Antipsychotics and insulin are the most prescribed medications that cause weight gain. Where possible, alternative options such as SGLT2 inhibitors or GLP-1 RA should be considered for patients with type 2 diabetes. Consider using metformin to prevent weight gain caused by anti-psychotic medications as recommended in the Obesity Canada Clinical Practice Guidelines pharmacotherapy chapter.[3]

Finally, focus on optimizing lifestyle changes through behavioural support. Educate patients on modulators of the appetite system and the importance of stress management, high-quality sleep, and the role of their environment in weight management.

It is important to remind patients that the goal of the above-mentioned treatment modalities isn't solely weight loss but improving how they feel and their overall health. Often, re-defining success with behaviour goals (e.g., walking 5 blocks without shortness of breath) is more effective than emphasizing a number on the scale. Addressing these issues can often enhance patients' well-being and improve overall satisfaction with treatment.

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↓**20%**

(HR 0.80; 95% CI [0.66, 0.98])

(event n=174 vs. 213)

Non-fatal MI†

↓**30%**

(HR 0.70; 95% CI [0.59, 0.82])

(event n=237 vs. 332)

Non-fatal stroke†

↓**29%**

(HR 0.71; 95% CI [0.54, 0.94])

(event n=85 vs. 118)

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Please consult the Vascepa® Product Monograph at https://pdf.hres.ca/dpd_pm/00065525.PDF for important information relating to adverse reactions, drug interactions, and dosing/administration information which have not been discussed in this piece. The Product Monograph is also available by calling HLS Therapeutics Inc. at 1-833-266-3423.

*8,179 statin-treated adult patients with elevated serum triglyceride levels (≥1.5 mmol/L to <5.6 mmol/L) who were also at high risk for atherothrombotic events. Patients either had established CVD or were at high risk for CVD and were randomized to either Vascepa® or placebo. Patients with established cardiovascular disease were at least 45 years of age and had a documented history of coronary artery disease, cerebrovascular or carotid disease, or peripheral artery disease. Patients with other risk factors for cardiovascular disease were at least 50 years of age and had diabetes and at least one additional major cardiovascular risk factor. 5-point MACE was defined as time to first occurrence of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. Most patients at baseline were taking at least one other cardiovascular medication including anti-hypertensives (95%), anti-platelet agents (79.4%), beta blockers (70.7%), angiotensin-converting enzyme (ACE) inhibitors (51.9%), and angiotensin receptor blockers (ARB) (27.0%), with 77.5% taking either an ACE inhibitor or ARB. At baseline, while on stable background lipid-lowering therapy, the median LDL-C was 1.9 mmol/L.
†Incidence rates of CV events per 100 patient years (Vascepa® vs. placebo): cardiovascular death, 1.0 vs. 1.2; non-fatal myocardial infarction, 1.4 vs. 2.0; non-fatal stroke, 0.5 vs. 0.7.
‡CV death includes adjudicated cardiovascular deaths and deaths of undetermined causality.
§Comparative clinical significance has not been established.
CCS, Canadian Cardiovascular Society; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

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COPD 2024: APPLYING THE CANADIAN THORACIC SOCIETY (CTS) 2023 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) GUIDELINE FOR PREVENTING EXACERBATIONS, IMPROVING HEALTH STATUS, AND PREVENTING MORTALITY

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, chronic respiratory condition that is associated with the risk of morbidity and mortality. Approximately 2 million Canadians live with COPD, and as many as 1 million suffer while remaining undiagnosed and untreated.[1] COPD exacerbations represent the most expensive cause of hospitalization with the highest likelihood of hospital readmission.[1]

Exacerbations are the primary driver of mortality in patients with COPD. These exacerbations are the second leading cause of hospitalization in Canada with an average length of stay of 7 days.[2] In fact, 1 in 5 patients with COPD will die within 1 year of their first hospitalization due to an exacerbation.[3] For those 65 or older in Ontario, the overall 365-day mortality stands at nearly 28% following their first hospitalization due to an exacerbation.[4] The best indicator of the risk of future exacerbations is a history of exacerbations.

The time has come to end the stepwise pharmacologic escalation that has defined the treatment paradigm in COPD. The call to action is to shift from the slow promotion of inhaled pharmacotherapy based on exacerbations to a direct escalation to inhaled pharmacotherapy with demonstrated evidence to prevent the exacerbations.

What Are The Risk Factors and The Burden of Disease?

COPD is a disease characterized by persistent airflow limitation. The etiology revolves around exposure to combustion byproducts. This involves individuals with exposure to tobacco and cannabis smoke. This exposure can occur through either personal smoking or via passive second hand exposure. As well, electronic cigarettes are a growing concern as an etiologic agent due to the increase in airway inflammation that may lead to the development of COPD. In addition, COPD can be attributed to chronic exposure to biomass fuels and air pollution.[5] Those with exposure to household indoor air pollution, and ambient air pollution, as well as those with outdoor smoke exposure, are at an increased risk for the development of underlying COPD. Patients without a personal tobacco history, yet presenting with dyspnea, should be asked about their exposure to indoor air pollution, ambient outdoor pollution, or biomass exposure.

What Are The Key Indicators For Considering a Diagnosis of COPD?

In addition to chronic exposure to an etiologic agent, key indicators for consideration for COPD include the following: dyspnea that is progressive over time, persistent, or is characteristically worse with exercise; chronic cough and sputum production that may be intermittent, and while the cough may be dry, it is usually associated with a productive sputum component; individuals with a recurrent wheeze; and those with recurrent lower respiratory tract infections.

The diagnostic test for confirmation of COPD is a post-bronchodilator spirometry test. In those with COPD, this test demonstrates that less than 70% of the air can be exhaled from the lungs in the first second, indicated by a Forced Expiratory Volume in 1 second (FEV1)/ Forced Vital Capacity (FVC) ratio of <0.7 and absence of significant bronchodilator response. The severity of COPD, as determined by spirometry, is defined by the percent predicted post-bronchodilator FEV1.

How Can We Screen and Diagnose COPD More Effectively And Earlier In a Primary Care Setting?

COPD is irreversible and progressive, yet it marches in a steady, insidious manner that may blend into the background of life. Symptoms associated with COPD are often misconstrued as related to aging, deconditioning, or the steady decline of functional status that occurs with the passage of time.

Active screening for symptomatic individuals at risk of COPD is required for an early diagnosis of the condition. The Canadian Lung Health Test is a validated screening

Do you cough regularly?
Do you cough up phlegm regularly?
Do even simple chores make you short of breath?
Do you wheeze when you exert yourself or at night?
Do you get frequent colds that persist longer than those of people you know?[6]

tool to identify patients with possible COPD by screening those who are aged 40 years or older and are either currently smoking or former smokers who have a minimum 10 pack-year tobacco history. If they answer yes to one of the following questions, it is recommended that they undergo screening for COPD with post-bronchodilator spirometry.

If a patient responds yes to one or more of the Canadian Lung Health Test questions, screening for COPD with post-bronchodilator spirometry is recommended. In an outpatient screening cohort, 26% of patients who screened positive with the Canadian Lung Health Test received a new diagnosis of COPD. In addition, 93% of those newly-diagnosed patients had mild or moderate disease, notably capturing those early in the disease course.[7]

Is The Goal Exacerbation Reduction or Symptom Control or Both?

The goals of therapy for COPD involve the alleviation of dyspnea, improvement of health status, and an improved quality of life (**Figure 1**).[8] The foundation of COPD management across the entire disease spectrum involves self-management education. This involves several key components, including optimization of inhaler technique; inhaler review and subsequent re-review; assessment and review of medication adherence; breathing and cough techniques; as well as an understanding and early recognition of acute exacerbations of COPD with a documented action plan and its implementation. Complete cessation of tobacco use, or inhaled smoke exposure is paramount to slow the progression of COPD. Tobacco cessation carries a mortality benefit. Physical activity with regular daily exercise is essential to promote overall health and well-being. The recommended vaccines for individuals with COPD include the COVID-19 primary series, Pneumococcal, Respiratory Syncytial Virus, Pertussis, and Herpes Zoster.[5]

Inhaled maintenance medications, in addition to preventative pharmacotherapy, are recommended for all patients with COPD across the entire disease spectrum, with the goal of alleviating the symptom burden with respect to dyspnea and exercise tolerance, thereby enhancing the overall health status. Inhaled pharmacotherapy is fundamental in preventing acute exacerbations of COPD and in reducing mortality.

How Can We Best Identify Those With COPD Whose Disease Is Not Under Good Control and When Should We Escalate Their Treatment?

The 2023 Canadian Thoracic Society (CTS) guideline on pharmacotherapy **(Figure 2)** in patients with stable COPD presents an organized, evidence-informed approach that aligns effective treatments based on symptom burden, spirometry, and the risk of future exacerbations and mortality.[8]

The first step toward identifying evidence-based inhaled pharmacotherapy involves an assessment of the patient's symptom burden, lung function, and risk of exacerbation and mortality.

When assessing the symptom burden, the COPD Assessment Test (CAT), a validated 8-question tool, is used to assess the impact of COPD as a major medical condition impacting the patient's quality of life **(Figure 3)**. The CAT assesses domains such as cough, sputum, chest tightness, exertional dyspnea, activity limitation, confidence leaving the home, quality of sleep, and energy level. A CAT score of 10 or higher places the patient on the higher-risk side of the CTS algorithm, indicating a more moderate and severe burden of disease.

If the CAT score is not available, the modified Medical Research Council (MRC) breathlessness scale is a validated instrument for the assessment of symptom burden in COPD **(Figure 4)**. The key discriminator is the modified MRC grade of 2 for dyspnea. An individual at an MRC grade of 2 for dyspnea would comment that on level ground they walk slower than people of the same age because of breathlessness or they have to stop when walking at their own pace because of dyspnea. The key cutoff is a modified MRC grade of 2 or higher, indicating worse dyspnea, which places the patient on the moderate to severe side of the algorithm.

Patients are then stratified based on lung function. Mild COPD with a spirometric post-bronchodilator FEV1 of greater than or equal to 80% places patients on the milder, left side of the CTS COPD algorithm **(Figure 2)**. However, those with moderate COPD, or worse, have an FEV1 of less than 80%, are placed on the moderate to severe side of the algorithm.

Finally, exacerbation of COPD and mortality risk are assessed with a retrospective assessment of exacerbations that have occurred in the previous year.

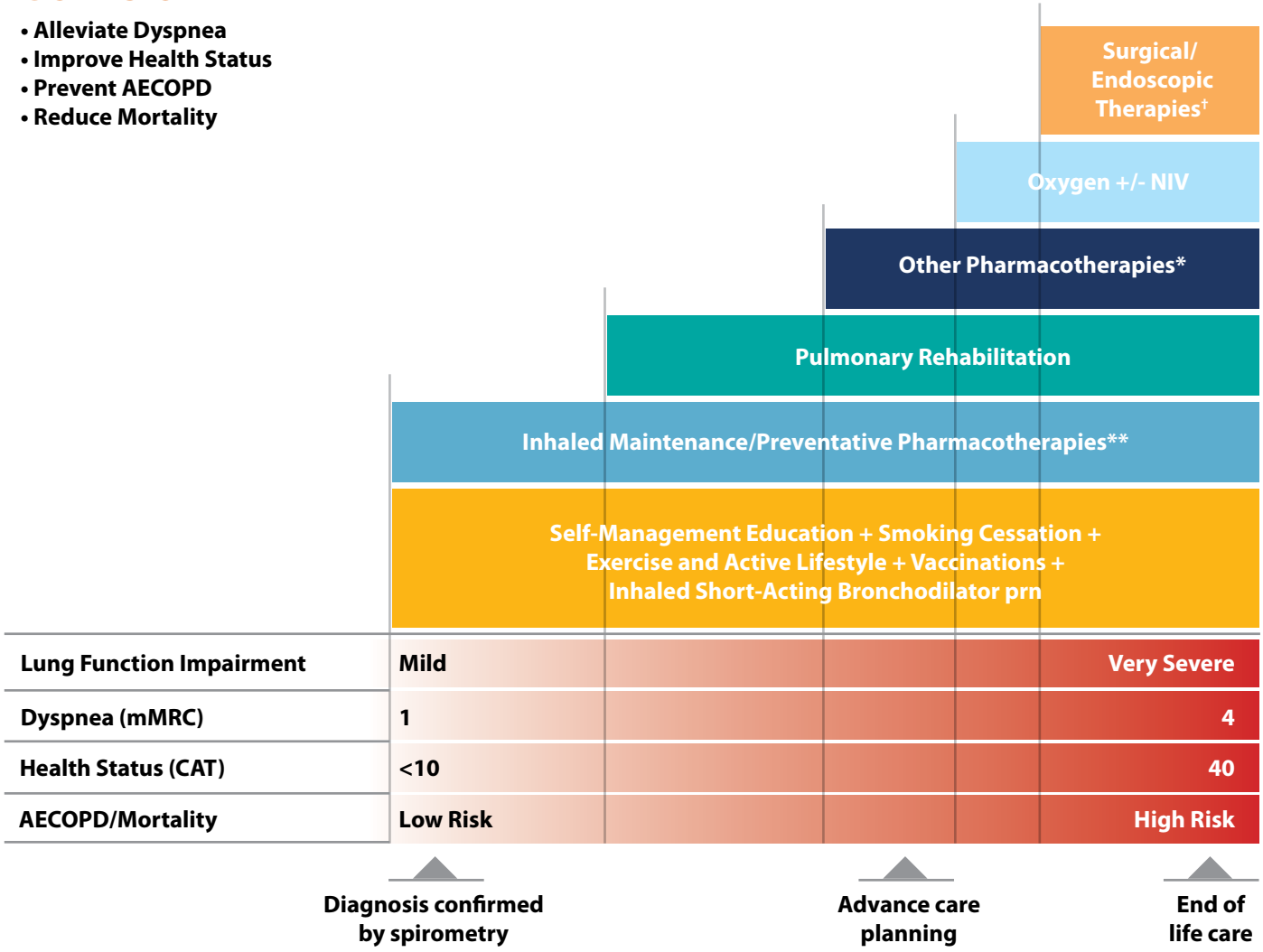

Figure 1. Integrated Comprehensive Management of COPD; *adapted from Bourbeau, J et al., 2023*

Integrated comprehensive management of COPD includes confirming COPD diagnosis with postbronchodilator spirometry, evaluation and on-going monitoring of dyspnea/symptom burden and risk of exacerbations and use of both pharmacologic and nonpharmacologic interventions (see Figure 3) to alleviate dyspnea/symptoms, improve health status, prevent AECOPD and reduce mortality. The approach should not be viewed as "stepwise" and may not necessarily occur in the order they appear for all patients. Self-Management Education includes optimizing inhaler device technique and [re-]review, assessment and review of medication adherence, breathing and cough techniques, early recognition of AECOPD, written AECOPD action plan and implementation (when appropriate), promoting physical activity and/or exercise, and other healthy habits including diet and smoking cessation.

† Surgical therapies may include lung transplantation and lung volume reduction (including with endoscopic valves).

* Other pharmacotherapies include oral therapies (prophylactic macrolide, and PDE-4 inhibitor, mucolytic agents for patients with chronic bronchitis), alpha-1-anti-trypsin augmentation therapy for documented severe A1AT deficiency, and opioids for severe refratory dyspnea (see prior CTS Guideline).

** Inhaled Maintenance/Preventative Pharmacotherapies are long-acting muscarinic antagonists (LAMA) and/or long-acting β2-antagonists (LABA) with or without inhaled corticosteroids (ICS). ICS montherapy should NOT be used in COPD management.

Abbreviations: A1AT= alpha-1 antrtrypsin; **AECOPD =** acute exacerbation of COPD; **CAT=** COPD assessment test; **COPD =** chronic obstructive pulmonary disease; **CTS =** Canadian Thoracic Society; **mMRC =** modified Medical Research Council; **prn =** as-needed; **NIV =** noninvasive ventilation.

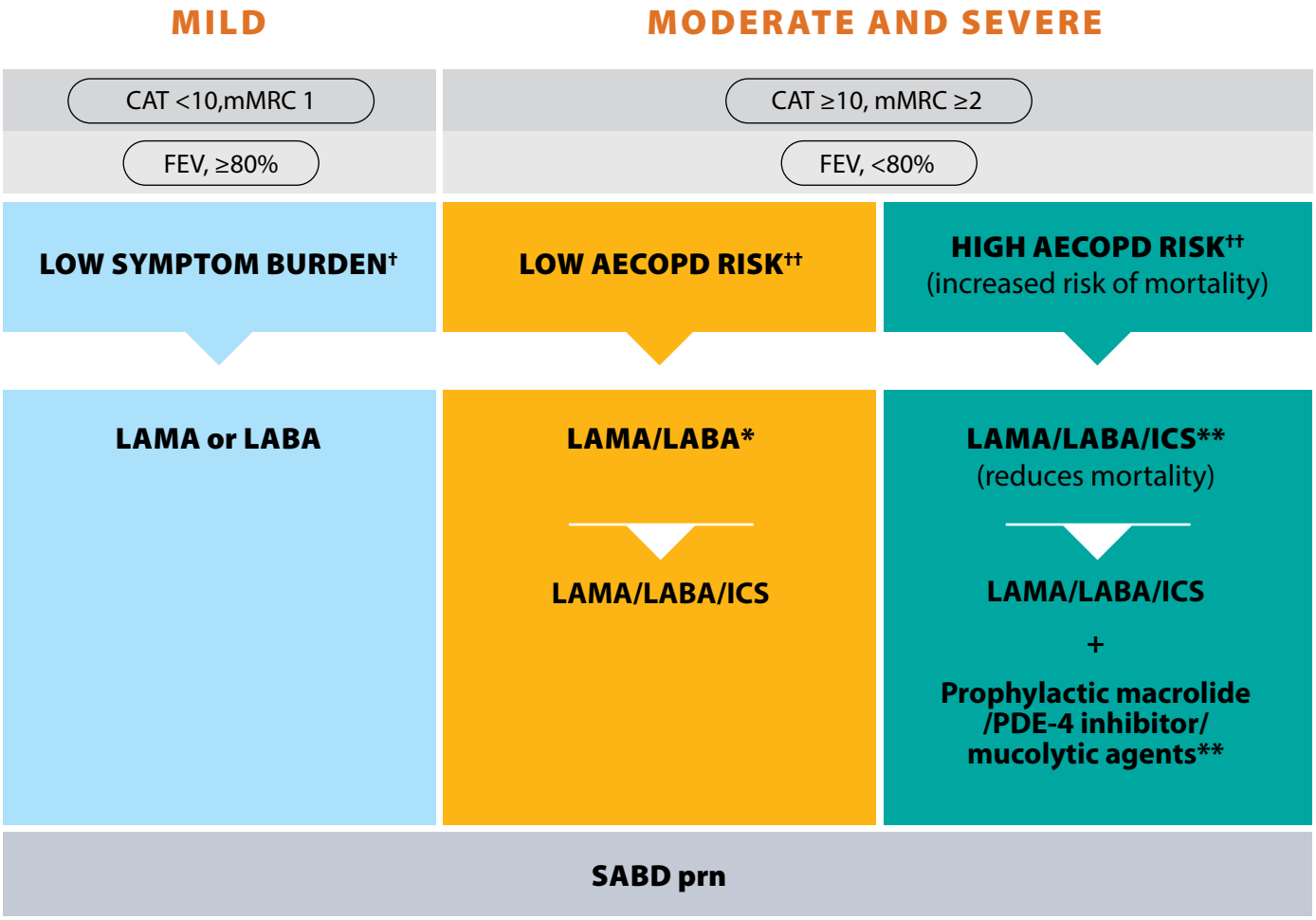

Figure 2. COPD Pharmacotherapy; *adapted from Bourbeau, J et al., 2023*

This figure promotes an evidence-informed approach that aligns proven effective treatments with spirometry, symptom burden, risk of future exacerbations and mortality risk. Because of the clinical heterogeneity in COPD, spirometry should not be used in isolation to assess disease severity and this is why it is also important to perform a thorough clinical evaluation of the patient, including symptom burden and risk of exacerbations that permits the implementations of treatments that are specific for subpopulations. SABD prn (as needed) should accompany all recommended therapies across the spectrum of COPD.

† Symptom burden encompasses shortness of breath, activity limitation, and impaired health status.

†† Individuals are considered at "Low Risk of AECOPD" if ≤1 moderate AECOPD in the last year (moderate AECOPD is an event with prescribed antibiotic and/or oral corticosteroids) and did not require hospital admission/ED visit).

* LAMA/LABA single inhaled dual therapy is preferred over ICS/LABA inhaled combination therpay considering the additional improvements in lung function and the lower rates of adverse events such as pneumonia. ISC/LABA combination therapy should be used in individuals with concomitant asthma. There is no universally accepted definition of concomitant asthma. The 2017 CTS Position Statement on COPD Pharmacotherapy provides guidance on the assessment of patients who may have concomitant asthma.

** Triple inhaled ICS/LAMA/LABA combination therapy should preferably be administered in a single inhaler triple therapy (SITT), and not in multiple inhalers (see text), although we acknowledge that some patients continue to prefer separate inhalers. *Oral pharmacotherapies in this group include prophylactic macrolide, and PDE-4 inhibitor and mucolytic agents for patients with chronic bronchitis.

Abbreviations: CAT = COPD assessment test; **mMRC =** Modified Medical Research Council; **SABD prn =** short-acting bronchodilator as needed; **AECOPD =** acute exacerbation of COPD; **ED =** emergency department; **LAMA =** long-acting muscarinic antagonist; **LABA =** long-acting β2-antagonist; **ICS =** inhaled corticosteroid.

These exacerbations are acute, trajectory-altering events in the life of a patient with COPD that are characterized by increasing dyspnea, sputum volume, sputum purulence, and symptom burden. In a patient with COPD, the term chest infection is a disservice; exacerbation of COPD is the appropriate descriptor. Mild COPD exacerbations are typically managed on an outpatient basis, and do not require escalation of maintenance inhaled therapy, yet they do require the use of a reliever medication, almost universally a short-acting beta agonist (SABA). Moderate COPD exacerbations require outpatient pharmacotherapy involving an oral corticosteroid alone or in combination with antibiotic therapy if there is an infectious exacerbation. Severe COPD exacerbations are defined as those requiring an emergency department visit or admission to hospital/ICU.

Those at low risk of acute exacerbations of COPD are those who, in the past year have had at most one moderate exacerbation that was managed on an outpatient basis and have not had a severe exacerbation. Those at high risk for exacerbation and mortality are those that have had 2 or more moderate exacerbations that were managed on an outpatient basis, or one or more severe exacerbations.

Fundamental to this algorithmic approach of pharmacotherapy in COPD is the recognition that higher-risk features take precedence over lower-risk features. An individual with a low symptom burden along with a high-risk exacerbation history would be defined within the algorithm by the higher-risk feature. The higher-risk features take precedence over the lower-risk features when proceeding through the algorithm to identify the appropriate COPD pharmacotherapy.

What About Mild COPD?

As mentioned previously, mild COPD is characterized by a spirometric post-bronchodilator FEV1 that is greater than or equal to 80% and a low symptom burden with a CAT

Figure 3. COPD Assessment Test; adapted from https://www.catestonline.org

score of less than 10 or a modified MRC grade of dyspnea of 0 to 1. While patients with mild COPD present with a low symptom burden and an absence of exacerbations, fundamentally they possess a fixed, chronic, progressive obstructive lung disease. The era of SABA-only therapy for mild COPD is over. SABA therapy is necessary for all patients across the spectrum of COPD; however, this therapy is insufficient. Patients with mild COPD should be placed on long-acting bronchodilator therapy with a long-acting muscarinic antagonist (LAMA) or a long-acting beta agonist (LABA). There is evidence that the use of LAMA therapy in early-stage COPD can attenuate the rate of decline of lung function and reduce the frequency of exacerbations.[9] Thus, the foundation of inhaled COPD therapy involves long-acting bronchodilator therapy, and those with mild disease deserve this therapy at a minimum.

What Is The Evidence For Dual Versus Triple Therapy?

In a patient population actively screened for COPD, close to 50% of patients will have moderate spirometric disease, and moderate or worse disease will constitute between 70 to 80% of patients.[10,11] Frequent exacerbations of 2 or more per year, will occur in approximately a quarter of patients. Nearly three-quarters of patients have infrequent exacerbations with at most 1 exacerbation in the previous year.[12]

Individuals with a low risk of acute exacerbations of COPD along with a moderate to high symptom burden, characterized by health status impairment with a CAT score of 10 or higher, or a modified MRC grade of 2 or higher for dyspnea, and a moderate or worse spirometric COPD, should be initiated on dual bronchodilator therapy.

The subset of individuals with symptomatic COPD and a moderate to high symptom burden, characterized by a modified MRC grade of 2 or higher for dyspnea, constitute a sizable proportion of patients seen in clinical practice.[13]

The foundation of management for this large subset of those with symptomatic yet infrequently exacerbating COPD is dual bronchodilator therapy. The CTS guideline places patients with moderate or worse spirometric disease and a high symptom burden characterized by the CAT or modified MRC in the centre of our algorithm for a good reason. The minimum therapy for symptomatic COPD with a high symptom burden or a moderate to worse spirometry-confirmed severity with infrequent exacerbations is dual bronchodilator therapy.

If dual bronchodilator therapy is insufficient for addressing the symptom burden, or if in the future this therapy becomes insufficient, or if an exacerbation occurs, patients should be escalated to single inhaler triple therapy. Compared to the previous iteration of our guidelines in 2019, the backward arrows permitting de-escalation of inhaled therapy have been removed.[14] Though this patient population may not experience frequent exacerbations, if dual bronchodilator therapy is insufficient for controlling the symptom burden, becomes insufficient, or an exacerbation occurs, escalation to triple therapy is recommended. The Kronos clinical trial, which included a significant proportion of patients (74%), who have not had an exacerbation in the previous year, demonstrated a lower likelihood of exacerbation for those on triple therapy versus those on dual bronchodilator therapy.[15]

Who Should Have Triple Therapy, and Why?

Your friendly neighbourhood Respirologist is likely a frequent prescriber of single inhaler triple therapy in COPD, but this is expected given the severity of patients they co-manage with primary care. With only approximately a quarter of COPD patients experiencing frequent exacerbations,[12] triple therapy is reserved for those for whom dual bronchodilator therapy is insufficient at managing their symptoms, or if they have experienced

Grade	Description of breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards [91 meters] or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

Figure 4. Modified Medical Research Council dyspnea scale; Adapted from: Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J 1959; 2:257.

an exacerbation on dual bronchodilator therapy. Triple therapy is also reserved for those at higher risk of future exacerbations and mortality, as indicated by those who have experienced 2 or more moderate exacerbations in the previous year or 1 or more severe exacerbations. In this cohort with frequent exacerbations, single inhaler triple therapy has demonstrated evidence of significant exacerbation reduction compared to dual bronchodilator therapy, as well as data indicating an all-cause mortality reduction. De-escalation from single inhaler triple therapy is not recommended. Initial pharmacotherapy with less than triple therapy for this group of patients who frequently experience exacerbations is not recommended. These patients deserve inhaled therapy with demonstrated evidence to prevent the exacerbation events driving their high-risk phenotype.

Mild COPD Example:

43 years of age

Chief complaint: Shortness of breath when climbing stairs and occasional morning cough and sputum.

A 22 pack-year tobacco history, morning chronic bronchitis phenotype, absence of exacerbations, a modified MRC grade of 1 for dyspnea. Post-bronchodilator spirometry demonstrating mild COPD with an obstructed ratio of 0.64 and an FEV1 of 84%. **Recommended initial pharmacotherapy:** LAMA or LABA with a SABA reliever.

Moderate Spirometric COPD With Infrequent Exacerbations Yet a High Symptom Burden

52 years of age

Chief complaint: Shortness of breath when walking with spouse and with weekend activities such as grocery, shopping, and indoor chores.

A 27 pack-year tobacco history, morning chronic bronchitis phenotype, a modified MRC grade of 2 for dyspnea with a CAT score of 19, with 1 outpatient lower respiratory tract infection treated at a walk-in clinic with an antibiotic within the past 12 months. Post-bronchodilator spirometry demonstrating moderate COPD with an obstructed ratio of 0.57 and an FEV1 of 64%. **Recommended initial pharmacotherapy:** LAMA/LABA dual bronchodilator therapy with a SABA reliever.

Frequently Exacerbating COPD With a High Symptom Burden and Moderate Airway Obstruction

61 years of age

Chief complaint: Requested a primary care physician follow-up appointment to review the emergency department visit for a chest infection requiring an antibiotic and prednisone.

A 31 pack-year tobacco history, morning chronic bronchitis phenotype, a modified MRC grade of 2 for dyspnea with a CAT score of 15, with 1 exacerbation treated in the emergency department on an outpatient basis in the past 12 months with an antibiotic and prednisone. Post-bronchodilator spirometry demonstrating moderate COPD with an obstructed ratio of 0.59 and an FEV1 of 71%. **Recommended initial pharmacotherapy:** LAMA/LABA/ICS single inhaler triple therapy.

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K.L.: None declared

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MANAGEMENT AND TREATMENT OF RED EYES IN PRIMARY CARE

Introduction

Red eyes are a common complaint in primary care settings, with a plethora of causes and implications. Some etiologies are benign and self-limiting, while others are sight threatening and require urgent referral to an ophthalmologist. Therefore, it is important for primary care physicians to be able to carry out a diligent eye exam, recognize the signs and symptoms of different types of red eye presentations, to initiate appropriate management and treatment and to refer to ophthalmology when needed.[1–5]

What Can't Be Missed in Primary Care and What Are The Most Common Entities?

Usually, the eye becomes red (hyperemia, injection) because of increased blood flow in the vessels of the conjunctiva, episclera, and/or sclera (due to trauma, chemical burns, or immune reactions), because of infections (by bacteria, viruses, parasites, or fungi), or because of the long-term impact to the outer eye related

to systemic diseases (such as Sjögren's syndrome).[6]

The most common causes of red eyes in primary care are **conjunctivitis, dry eye syndrome, blepharitis, episcleritis, and subconjunctival hemorrhage.**[1,2] These conditions are usually benign and can be managed with topical medications, lubricants, and hygiene measures. However, some of these conditions may be recurrent or associated with systemic diseases, such as diabetes, rheumatoid arthritis, other autoimmune syndromes, or infections, and may require a referral to an eye care specialist for further investigation and treatment.[3]

The most serious causes of red eyes that require urgent referral to ophthalmology or hospital are **acute angle-closure glaucoma, hyphema, foreign bodies, corneal abrasions, or ulcers, scleritis, uveitis, endophthalmitis, orbital cellulitis, and open globe.**[7] These conditions can cause severe pain, vision loss, and permanent damage to the eye if not treated promptly. Therefore, it is essential for primary care physicians to be able to identify the red flags that indicate a potential emergency, such as:[7–9]

- Recent history of trauma or intraocular surgery
- Symptoms, such as **acute or subacute:**
    - Severe ocular/periocular/retro-orbital pain or headache
    - Nausea or vomiting
    - Decreased visual acuity or visual field loss
    - Photophobia
    - Constant tearing
    - Diplopia
- Signs, such as **acute or subacute:**
    - Proptosis or lid swelling
    - Large subconjunctival hemorrhage after trauma
    - Sectorial blue/purple hue of the sclera (scleritis)
    - Chemosis (swelling of the conjunctiva)
    - Corneal opacity, infiltrate, ulceration, abrasion, edema
    - Hypopyon or hyphema
    - Peaked iris or positive Seidel sign
    - Relative afferent pupillary defect
    - Foreign body in conjunctiva/sclera, cornea or inside the globe

Disease	Typical findings (in addition to red eye)	Management (class equivalent)
Angle closure	High IOP, shallow anterior chamber, corneal edema, pain, nausea or vomiting	Acetazolamide 500 mg PO or IV once, drops q15 min x 3 doses: Timolol 0.5%, brimonidine 0.1%, brinzolamide 1%, latanoprost 0.005%
Corneal abrasion, ulcer, or foreign body (FB)	Corneal opacity, infiltrate, epithelial loss, FB in cornea, fluorescein staining, tearing, photophobia	Moxifloxacin 0.5% gtts q1h Dendrites: also start valacyclovir 500 mg TID PO
Hyphema	Layered blood in anterior chamber, recent trauma, anterior chamber cells, photophobia	Prednisolone 1 % drops Q2H, cyclopentolate 1% gtts TID, dexamethasone 0.1% ung QHS
Uveitis	Anterior chamber cells, pain, photophobia	Prednisolone 1 % drops Q2H, cyclopentolate 1% gtts TID, dexamethasone 0.1% ung QHS
Scleritis or necrotizing scleritis	Severe deep pain boring to back of eye or head, pain on eye palpation, thinning of sclera (purple hue)	Ibuprofen 400-600 mg TID-QID PO x 5 days
Endophthalmitis	Hypopyon, pain, anterior chamber cells, recent surgery/eye trauma	Moxifloxacin 0.5% gtts q1h, moxifloxacin 400 mg PO or IV daily, with cefazolin 1g IV q8h
Orbital cellulitis	Diplopia, pain with EOM, eyelid edema, proptosis	CT orbits with contrast, treat with ceftriaxone IV and flagyl
Open globe	Peaked iris, subconjunctival hemorrhage, conjunctival edema, Seidel positive, recent Trauma	Eye shield, pain and nausea meds, do not attempt to pull FB out, do not place an eye patch

Table 1. Ocular emergencies, findings and early management; *courtesy of Jamie Bhamra, MD*

When in doubt about the nature and the extent of the pathology, it is safer to put a clear shield over the affected eye, without an eye patch, as putting any pressure on the globe can extrude intraocular contents. In an ideal world, patients coming for a possible open globe would have a protective shield placed over the eye as soon as they enter your office or hospital.[8]

Table 1 describes main findings of these ocular emergencies and initial management that a primary physician may start before sending the patient to an ophthalmologist on call the same day. Consider postponing antibiotics if an ophthalmologist will be seeing the patient quickly as cultures may be required. Be sure to verify about allergies to medications.[7,8,10–12]

Understanding The Common Ophthalmologic Pathologies Seen In Primary Care Clinics, Their Treatment and Referral Timing

The following sections will provide brief description of common ophthalmologic pathologies that present as red eyes, along with their clinical features, diagnosis, management, and referral criteria.

In general, severe worsening, or persistent symptoms (including decreased vision) not responding to treatment, as well as uncertain diagnosis or management should trigger an ophthalmology referral for the following clinical entities.

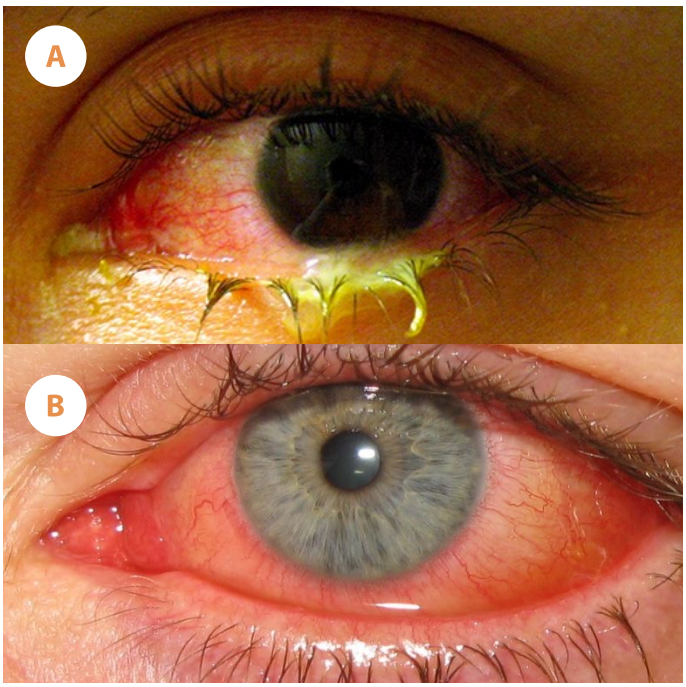


Figure 1: (A) A left eye with bacterial conjunctivitis. (B) A left eye with viral conjunctivitis. Note the lack of any significant purulent discharge in the viral case; *A: From CNX OpenStax, CC BY 4.0; B: From Marco Mayer, CC BY-SA 4.0.*

Conjunctivitis

Conjunctivitis is inflammation of the conjunctiva, a thin membrane covering the white part (sclera) of the eye and the inner surface of the eyelids. It can be caused by various agents, such as bacteria, viruses, allergens, or irritants.[13]

Main symptoms of conjunctivitis are redness, discharge, tearing, itching, burning, and foreign body sensation.[8]

Management of conjunctivitis depends on the type and severity of the condition. Bacterial conjunctivitis (*Figure 1A*) are usually swabbed to confirm the responsible organism (i.e., *Staphylococcus aureus, Staphylococcus epidermidis, Haemophilus influenzae, Streptococcus pneumoniae*, or *Moraxella catarrhalis*), and they are treated empirically with commonly available topical antibiotics. Gonococcal (superacute) or Chlamydial (chronic) conjunctivitis are considered and treated as sexually transmitted infections requiring reporting. Viral conjunctivitis (*Figure 1B*), from common cold viruses, are usually self-limiting and do not require specific treatment, but the following is recommended: isolation for up to 2 weeks or until symptoms resolve, frequent hand hygiene, wiping down frequently used surfaces and avoiding touching the eyes, sharing towels and pillowcases. Herpetic viruses (VZV, HSV1, HSV2) may need oral (or topical) antivirals, such as acyclovir or valacyclovir. Steroid and/or antibiotic topical regimens are typically not recommended in viral conjunctivitis. Allergic conjunctivitis are treated with cool compresses, chilled artificial tears, topical (and oral, if severe) antihistamines, antihistamines/mast cell stabilizer combinations, or corticosteroids (if severe), such as olopatadine, ketotifen, or loteprednol, for 2 to 4 weeks. Vasoconstrictors are never recommended in conjunctivitis.[8,14,15]

In addition to the above general referral criteria cited above, patients with conjunctivitis should be immediately

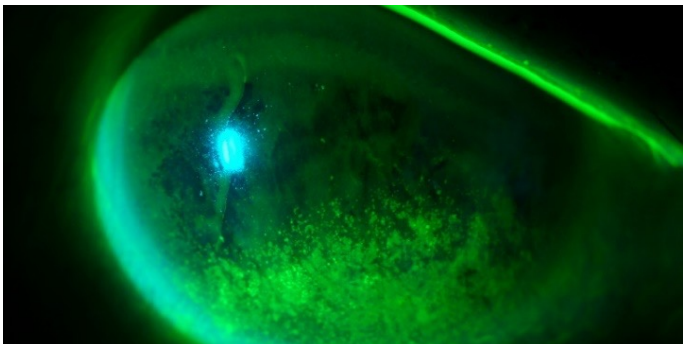


Figure 2: A cornea with punctate epithelial erosions (PEEs). These represent areas of epithelial cell loss and therefore stain positively with fluorescein. PEEs are evidence of ocular surface dryness. The distribution of the PEEs helps determine the underlying etiology. Inferior PEE, as seen above, can be secondary to exposure, chronic blepharitis, or trichiasis. This patient underwent multiple eyelid surgeries resulting in exposure keratopathy; *from Stefani Karakas, CC BY-NC-ND 3.0.*

referred for:[8,9]

- Suspected Gonococcal, herpes simplex (HSV) or zoster (VZV) infection
- Pre-existing ocular disease or immunocompromise
- Neonatal conjunctivitis.

Dry Eye Syndrome

Dry eye syndrome is a condition resulting from insufficient or poor-quality tears failing to lubricate and protect the ocular surface.[16] Two major forms are described (evaporative and aqueous-deficient) which can be caused by numerous factors, such as aging, hormonal changes, loss of tear film producing glands, increased focussed work (e.g., screens, books, driving), medications, systemic diseases, environmental conditions, or eyelid abnormalities (*Figure 2*).[17] The main symptoms of dry eye syndrome, which are usually worse at the end of the day, are tiredness, redness, burning, grittiness, foreign body sensation (sometimes sudden), tearing, light sensitivity, fluctuating, and decreased vision.[8]

General principles of treatment are to address underlying cause(s), supplement the tear film, prevent tear film loss, and protect the ocular surface. Treatments commonly used for dry eye syndrome include, primarily, eyelid hygiene, warm compresses, eyelids massages and frequent blinking (especially during focussed work). Artificial tears are helpful for acute symptoms and should be preservative-free if used more than QID.[9,18]

In addition to the above general referral criteria cited above, patients with dry eyes should be referred for:

- Suspected systemic disease association (e.g., Sjogren's syndrome)
- Continuous discomfort
- Exacerbation of symptoms.

Blepharitis

Blepharitis is inflammation of the eyelid margins and can be classified as anterior, posterior, or mixed.[19]

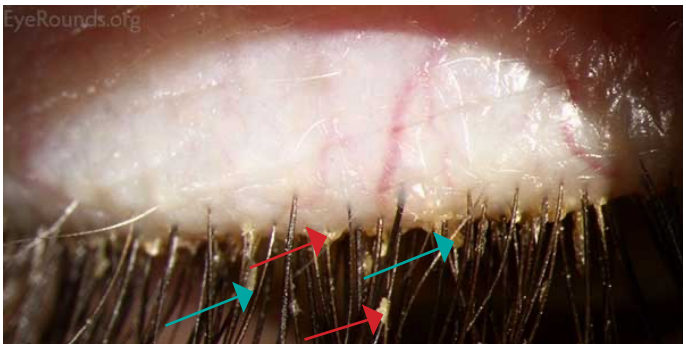


Figure 3: An upper lid with anterior blepharitis. Eyelid scaling or scurf (red arrows), typical of seborrheic blepharitis, have an oily or greasy consistency. Eyelash sleeves (green arrows), referred to as cylindrical dandruff, are typical of demodicosis. From Cindy Montague, CC BY-NC-ND 3.0. Arrows added for clarity

Anterior blepharitis affects primarily the base of the eyelashes and is caused by bacterial (staphylococcal) infections or seborrheic dermatitis (which can be accompanied by Demodex folliculitis – *Figure 3*). Posterior blepharitis, which primarily affects meibomian glands, is mainly caused by meibomian gland dysfunction.[9] Main symptoms of blepharitis, which are present upon awakening (in contrast to dry eyes – see above), are redness, scaling, crusting, itching, and burning of eyelids.[8]

Treatment of blepharitis aims to reduce bacterial load, remove the scales and crusts, improve meibomian gland function, and control inflammation and symptomatology. Commonly treatments for blepharitis include eyelid and eyelash cleansing, warm compresses (5-10 min) QD-BID and artificial tears QID. If signs and symptoms prevail, consider topical antibiotics (apply erythromycin ointment nightly on lashes) for 2 weeks, and next oral antibiotics (Doxycycline 100 mg BID) for 4-6 weeks.[20]

In addition to the above general referral criteria cited above, patients with blepharitis should be referred for:

- Complications, such as a chalazion or hordeolum not responding to conservative measures
- Eyelid malposition
- Suspected malignancy or other eyelid lesions
- Vascularization or marginal infiltrates of the cornea.

Subconjunctival Hemorrhage

Subconjunctival hemorrhage is bleeding collecting under the conjunctiva (*Figure 4*). It may be caused by numerous

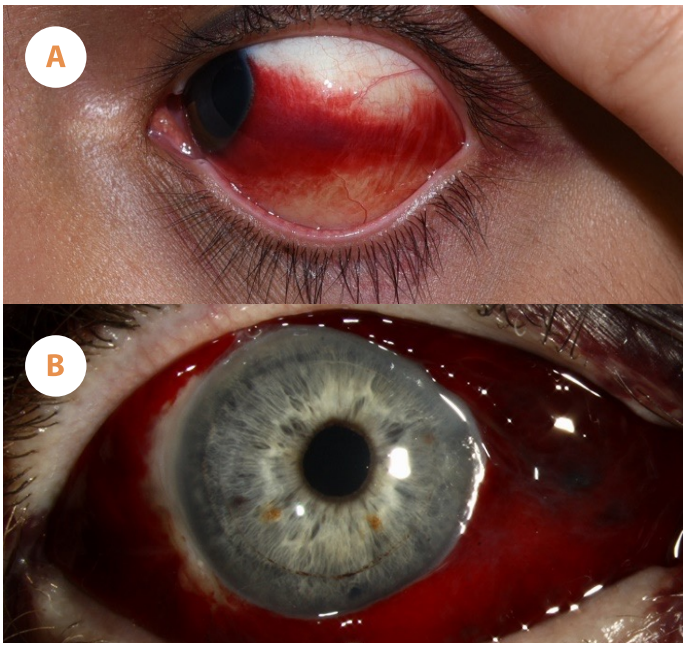


Figure 4: Subconjunctival haemorrhages can present as (A) small and localised or (B) large and diffuse. The amount and distribution of blood do not typically affect the management, which will be conservative and supportive; A: From Audrey C. Ko, MD, CC BY-NC-ND 3.0; B: From Toni Venckus, CC BY-NC-ND 3.0.

factors, such as trauma, coughing, sneezing, straining, hypertension, bleeding disorders, or use of anticoagulant medications.[21–23] The main sign of subconjunctival hemorrhage is a bright red patch on the white part of the eye, usually painless and not affecting vision. Mild tenderness may occur and resolves in 1-2 days.

Management of subconjunctival hemorrhage is conservative and supportive, as the condition is self-limited and usually does not require specific treatment. Treatments commonly used for subconjunctival hemorrhage include artificial tears, cold compresses, and sometimes analgesics, to relieve discomfort and to prevent dryness, exposure, and irritation. Subconjunctival hemorrhage usually resolves within 1 to 2 weeks, as blood is gradually absorbed by the body. Stopping blood thinners for this condition is not usually recommended or necessary.[8]

In addition to the above general referral criteria cited above, patients with subconjunctival hemorrhage should be referred for:

• Suspicion or recent history of ocular or orbital trauma.

Episcleritis

Episcleritis is a condition causing inflammation and redness of episclera, which is most superficial layer of the sclera, beneath the conjunctiva (*Figure 5A*). It usually affects one eye, sometimes both, may present with a discrete inflamed nodule, and occurs in a sectoral or diffuse pattern. Episcleritis is mild and often goes away on its own without treatment but tends to recur. It can cause discomfort, tearing, and sensitivity to light. It is sometimes associated with ocular surface problems or autoimmune disorders, such as rheumatoid arthritis, lupus, or Crohn's disease.[24] Episcleritis must be carefully distinguished from scleritis (*Figure 5B*), a more severe inflammation of deeper layers of the sclera leading to possible permanent eye damage if not treated promptly.[24] Scleritis presents with a high level of deep, boring pain and severe tenderness, even to light touch. Additionally, since scleral vascular dilation lies deeper, eye redness does not go away after instillation of phenylephrine drops and these dilated vessels are not mobile with a cotton tip. [8,9]

Episcleritis is treated with chilled artificial tears, cold compresses, and anti-inflammatory drugs, such

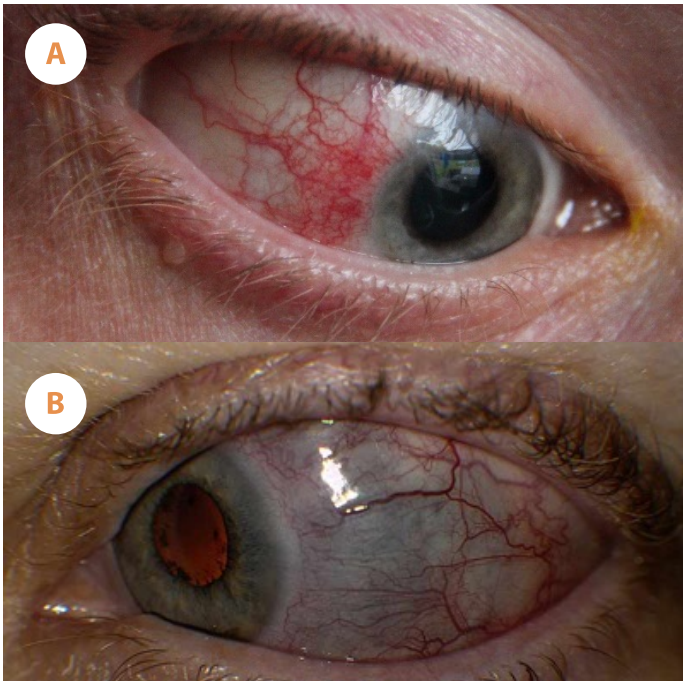


Figure 5: (A) Right eye with sectoral episcleritis. Episcleral inflammation is superficial and will typically blanch with the application of topical phenylephrine 2.5%. (B) A left eye with scleritis in a patient with rheumatoid arthritis. In contrast to episcleritis, scleral inflammation lies deeper and typically presents with a violaceous hue under natural light, which suggest thinning of the sclera; *A: From Asagan, CC BY-SA 3.0; B: From Cindy Montague, CC BY-NC-ND 3.0.*

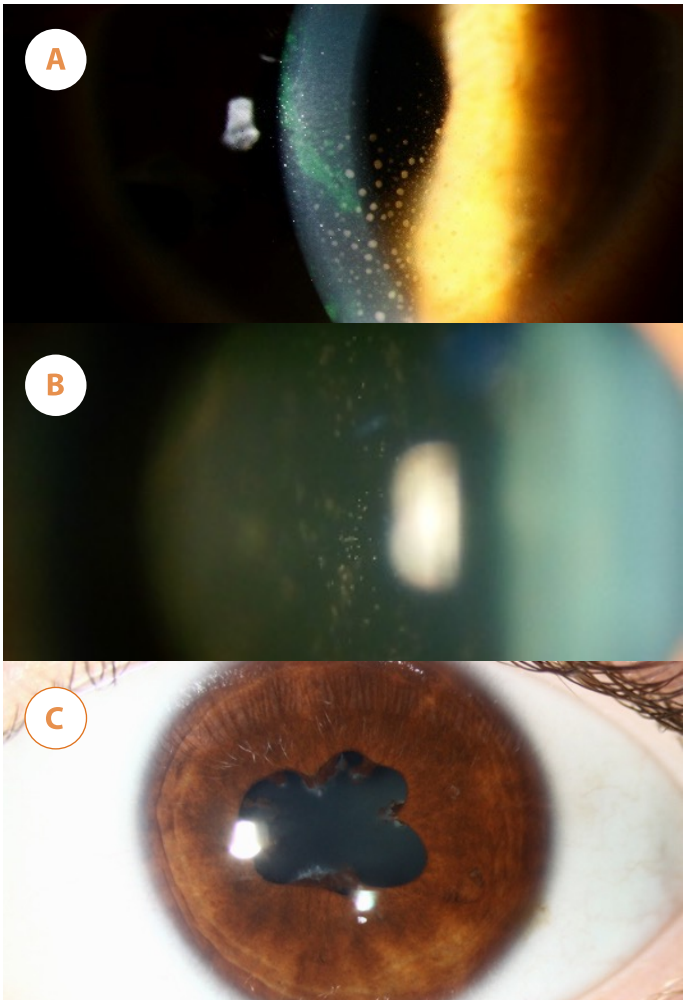


Figure 6: Three typical findings in anterior uveitis, from front to back: (A) keratic precipitates on the corneal endothelium, (B) white blood cells in the anterior chamber and (C) irregular, poorly reactive pupil due to posterior adhesion (synechiae) of the iris to the lens capsule.; *A: From Stefani Karakas, CC BY-NC-ND 3.0; B: From Imrankabirhossain, CC BY-SA 4.0; C: From Toni Venckus, CC BY-NC-ND 3.0.*

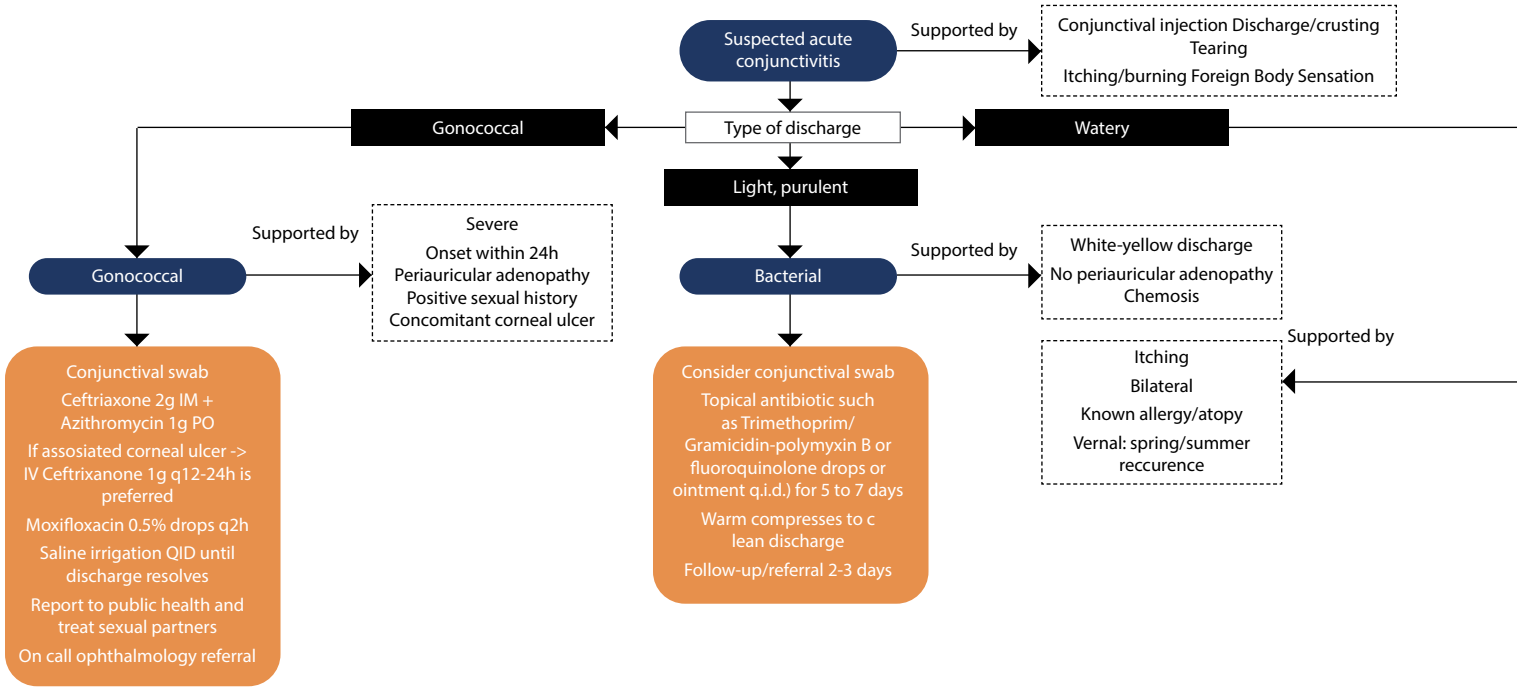


Figure 1. Algorithm for the management of conjunctivitis; *courtesy of Jamie Bhamra, MD*

as ibuprofen (400-600 mg TID-QID PO x 5 days) or corticosteroid eye drops (Fluoromethalone 0.1% gtts 4-6 x / day). Episcleritis usually resolves within 1-2 weeks, but it may recur. [8]

In addition to the above general referral criteria cited above, patients with episcleritis should be referred for:

- Recurrent or bilateral episcleritis
- Suspected scleritis
- Evidence of systemic disease or infection

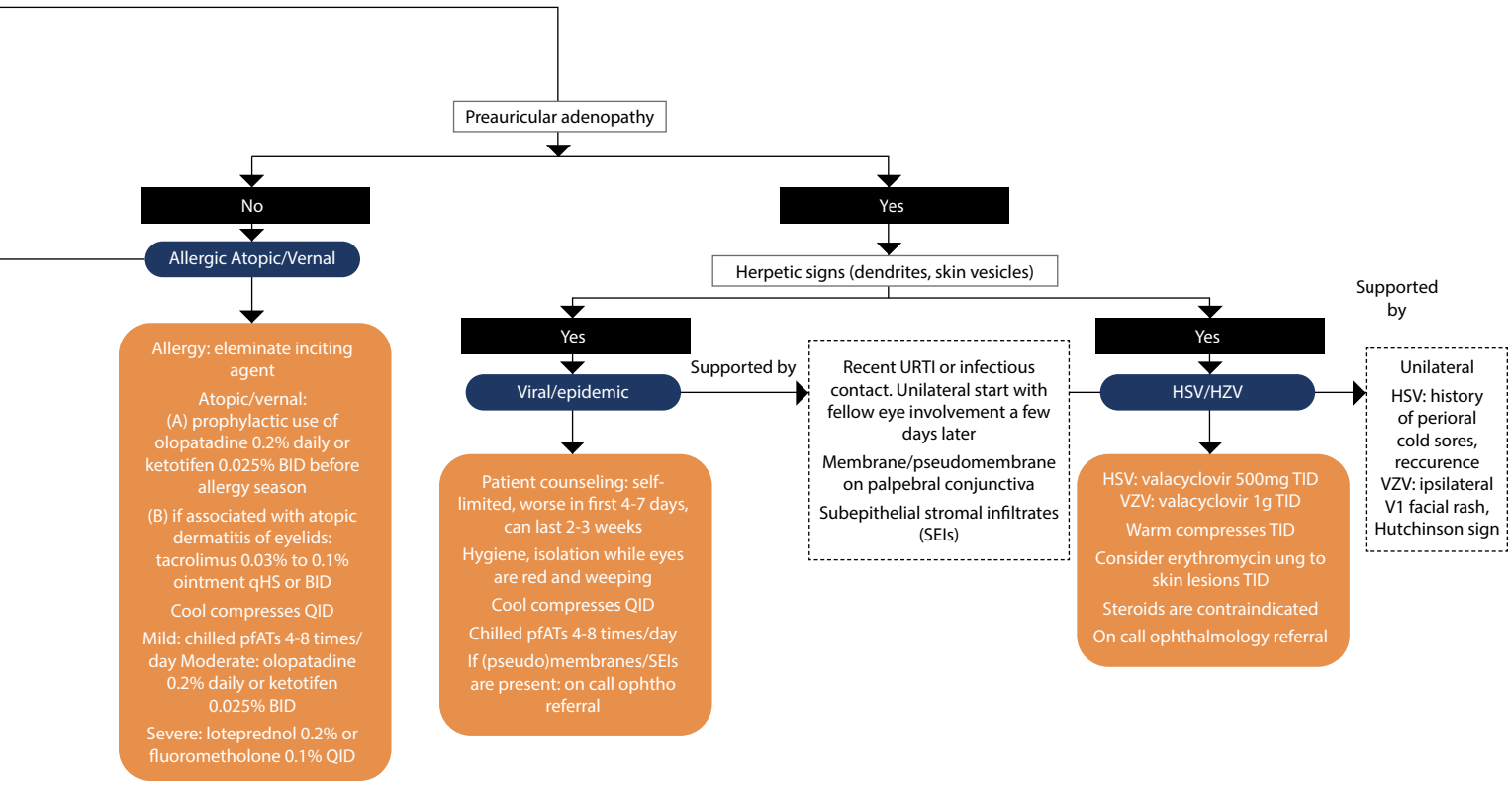
Uveitis

Uveitis describes a group of inflammatory conditions affecting the uvea, the "middle layer" of the eye composed of the iris (anterior), the ciliary body (intermediate), and the choroid (posterior). Etiologies of uveitis may be infectious or non-infectious. Infectious uveitis is caused by various microorganisms, such as bacteria, viruses, fungi, parasites, or protozoa, invading the eye directly or spread from a systemic infection. Non-infectious uveitis is associated with various systemic or ocular conditions, such as autoimmune diseases, neoplastic processes, trauma or surgery. In many cases, the cause of uveitis is unknown (idiopathic uveitis).[25]

Symptoms of uveitis vary on type and location of the inflammation and include eye pain and photophobia (worse in anterior uveitis, yet minimal in intermediate or posterior uveitis), blurred vision (mild to moderate in anterior uveitis, usually more severe in posterior uveitis), and floaters (clumps of vitreous cells in intermediate or posterior uveitis). Anterior uveitis, also called iritis, is more prevalent and usually causes more eye redness.[8]

Anterior chamber cells or white deposits on the corneal endothelium (keratic precipitates [KPs]) on slit lamp examination are almost pathognomonic for anterior uveitis (*Figure 6*). If a slit lamp is not available, detailed medical history and careful review of systems are necessary to find symptoms associated with systemic, immune-mediated diseases. These symptoms include fevers, chills, fatigue, malaise, cough, dyspnea, arthritis, diarrhea, blood in stool/urine, skin rashes, and oral/genital ulcers.[8] Sometimes, KPs may be viewed with direct illumination from a penlight or through a red reflex with by a direct ophthalmoscope. Irregular, poorly reactive pupils are also clues of possible anterior uveitic processes. Another helpful sign is consensual photophobia: in patients with unilateral uveitis, shining a bright light in the unaffected eye will induce pain in the affected eye.[7]

Uveitis can cause significant ocular morbidity and vision loss, especially when not diagnosed and treated promptly. Primary care providers should focus on identifying the condition, initiating first-line therapy, and



immediately referring to an eye specialist on call. More urgent considerations should be made for delayed or inadequate treatment, frequent recurrences or chronicity, involvement of both eyes, intermediate, posterior or panuveitis, association with systemic diseases or ocular comorbidities, and development of complications such as cataract, glaucoma, or retinal detachment.[25]

Conclusions

Red eyes are a common and challenging problem in primary care settings requiring careful, systematic, and comprehensive approach for accurate diagnosis and treatment. The primary care physician can become very familiar with common and serious ophthalmologic conditions presenting with red eyes. Moreover, primary care providers can be well suited to determine when a patient with a red eye requires the prompt attention of an eye specialist on call. We strive that, by using key points discussed above, our primary care colleagues feel better equipped and comfortable in providing optimized care for patients with common and emergency red eye presentations.

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NAVIGATING THE MAZE: A MINI-GUIDE FOR THE MANAGEMENT AND THERAPY OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Abstract

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), formerly known as Nonalcoholic Fatty Liver Disease (NAFLD), poses a significant global health challenge with a prevalence of 30% worldwide. Alarming projections anticipate a substantial increase in MASLD cases, highlighting the urgent need for preparedness and effective policies. The pathophysiology of MASLD involves a complex interplay of metabolic, genetic and lifestyle factors. Although liver biopsy remains the gold standard for the diagnosis of MASLD, non-invasive methods such as abdominal ultrasound, transient elastography with controlled attenuation parameter, shear wave elastography, and non-invasive serum fibrosis scores have been developed and validated. Effective risk stratification in primary care with non-invasive fibrosis scores, such as fibrosis 4 (FIB-4) index and NAFLD fibrosis score (NFS), optimizes healthcare resource utilization, ensuring appropriate referrals for high-risk patients while minimizing unnecessary referrals. Lifestyle intervention, including diet and physical activity, remains the primary therapy for MASLD. Notably, with the FDA approval of resmetirom, the first authorized medication for fibrotic metabolic dysfunction-associated steatohepatitis (MASH), and several antifibrotic agents under investigation, the therapeutic landscape for MASLD is rapidly evolving. Despite its increasing prevalence, morbidity and mortality, MASLD is frequently underdiagnosed in primary care. In this review, we aim to provide primary care physicians an update on the diagnosis, management and treatment of MASLD.

Introduction

With a 30% prevalence in Canada and globally, metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), is the most common liver disease worldwide.[1] Projection studies depict a concerning scenario, with Canadian data foreseeing a 20% MASLD case increase and up to a 95% rise in MASLD-related decompensated cirrhosis and hepatocellular carcinoma (HCC) incidence.[2] Is the world ready for the MASLD surge? This question led to the development of the MASLD Policy Preparedness Index. Surprisingly, no country scored above 50 out of 100, with Canada, which has no national MASLD management policy, ranking particularly low at 18.25 out of 100.[3]

Fighting this liver disease begins with establishing the most appropriate name and definition. Therefore, in June 2023, a multi-society Delphi consensus renamed NAFLD to MASLD, offering a positive definition highlighting the pathophysiologic link to metabolic disease and avoiding stigmatizing terms like "fatty".[4] MASLD is defined as evidence of fat in more than 5% of hepatocytes, with at least one cardiometabolic risk factor, without significant alcohol intake or other causes of steatotic liver disease, the new term covering all hepatic steatosis aetiologies **(Figure 1)**. The Delphi consensus process also introduced a new category, Metabolic Dysfunction and Alcohol Associated Liver Disease (MetALD), aiming to generate knowledge for a prevalent patient group with hepatic steatosis, with co-existing metabolic conditions and alcohol consumption exceeding the MASLD threshold (average daily 20 g-50 g for females, 30-60 g for males).[4] The clinical and histological spectrum of MASLD ranges from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), a necroinflammatory condition that eventually progresses to liver fibrosis – the hallmark event in the natural history of any liver disease leading to cirrhosis, liver failure and HCC.[5] MASLD extends beyond the liver, impacting extrahepatic organs and posing a well-established risk for all-cause mortality, especially cardiovascular disease-related mortality – the primary cause of death in MASLD.[6] In addition, patients with MASLD often experience mental, emotional and social challenges, resulting in impaired quality of life and a significant burden on healthcare resources.[7]

Despite the increasing prevalence of MASLD, with associated morbidity and mortality, real-world evidence shows underdiagnosis of MASLD in the primary care setting. This may be due to the lack of guidelines for screening for MASLD in primary care, the uncertainties associated with currently available diagnostic tests and pharmacotherapy.[8] The aim of this review is to provide an update on the pathophysiology, diagnosis, management, and treatment of MASLD for primary care physicians.

Pathophysiology and Risk Factors

MASLD pathogenesis is an intricate interplay of metabolic, genetic and lifestyle factors.[9] Insulin resistance is crucial

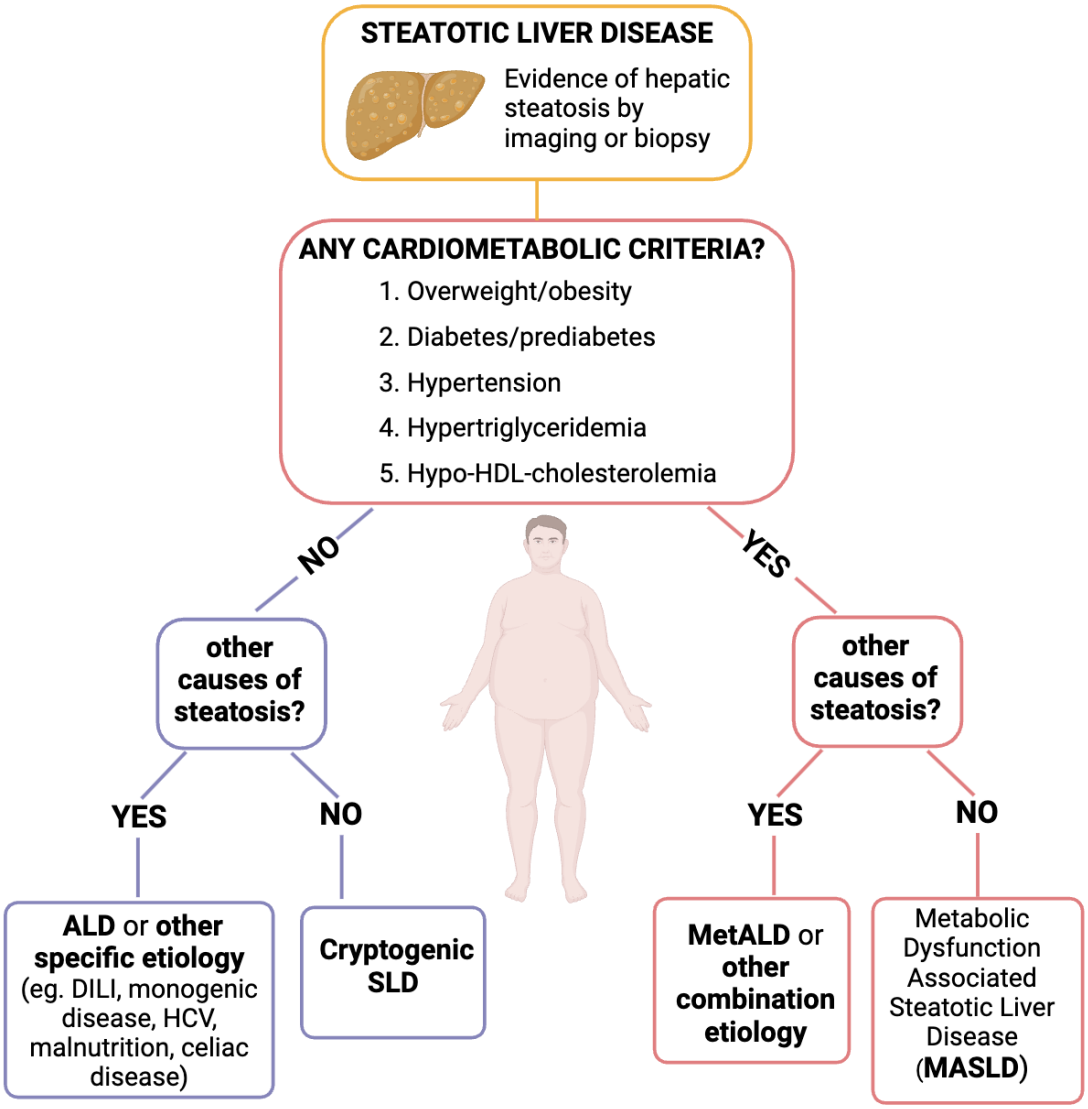

Figure 1. MASLD diagnostic criteria; *courtesy of Giada Sebastiani, MD, Felice Cinque, MD*

Cardiometabolic criteria: 1. Overweight defined as BMI ≥25 kg/m^2 [23 Asia] OR WC >94 cm (M) 80 cm (F) OR ethnicity adjusted equivalent; 2. Diabetes/prediabetes defined as fasting serum glucose ≥5.6 mmol/L [100 mg/dL] OR 2-hour post-load glucose levels ≥7.8 mmol/L [≥140 mg/dL] OR HbA1c ≥5.7% [39 mmol/L] OR T2DM OR treatment for T2DM; 3. Hypertension defined as blood pressure ≥130/85 mmHg OR specific antihypertensive drug treatment; 4. Hypertriglyceridemia defined as plasma triglycerides ≥1.70 mmol/L [150 mg/dL] OR lipid lowering treatment); 5. hypo-HDL-cholesterolemia (plasma HDL-cholesterol ≤1.0 mmol/L [40 mg/dL] (M) and ≤1.3 mmol/L [50 mg/dL] (F) OR lipid lowering treatment).

Abbreviations: ALD = alcohol-associated/related liver disease; **BMI =** body mass index; BP, blood pressure; **CMRF =** cardiometabolic risk factors; **DILI =** drug induced liver disease; **MetALD =** metabolic dysfunction and alcohol associated steatotic liver disease; **SLD =** steatotic liver disease; **WC =** waist circumference.

in MASLD, enhancing hepatic *de novo* lipogenesis and inhibiting adipose tissue lipolysis, causing liver steatosis.[10] It also promotes the production and release of adipokines and inflammatory cytokines, actively contributing to liver inflammation.[10] Visceral adipose tissue dysfunction, characterized by hypersecretion of adipokines and reduced levels of adiponectin, is also implicated in the pathogenesis of MASLD, as it increases oxidative stress and lipotoxicity.[11] Furthermore, alterations in gut microbiota are associated with MASLD, as increased intestinal permeability promotes increased fatty acid absorption and activates inflammatory pathways leading to liver inflammation.[12]

Notably, according to the multiple-hit hypothesis, MASLD development results from the convergence of various risk factors rather than a single causative agent.[9] First, as perfectly encoded in the new terminology, classic metabolic risk factors are associated with increased MASLD risk. Indeed, in patients with T2DM or obesity, MASLD prevalence rises to 50% and 90%, respectively.[1] Second, a genetic predisposition, particularly the I148M

polymorphism of PNPLA3 affecting triglyceride lipolysis in lipid droplets, variations in TM6SF2 influencing cholesterol metabolism, and alterations in MBOAT7, a key player in phospholipid metabolism, have been identified.[13] Third, lifestyle habits such as physical inactivity and an unhealthy diet rich in refined carbohydrates, fructose-containing beverages, saturated fats, and processed red meats, significantly contribute to MASLD onset and progression.[14] **Table 1** provides a list of risk factors for identifying patients at risk for MASLD and liver fibrosis.

Diagnostic Tools for MASLD, MASH and Related Fibrosis

Liver biopsy, the gold standard for diagnosing all three key features of MASLD (hepatic steatosis, steatohepatitis, and fibrosis), is currently the sole approved tool for diagnosing

Risk factor	Criteria
Dysglycaemia or type 2 diabetes	• Prediabetes: HbA1c 39-47 mmol/mol (5.7-6.4%) or fasting plasma glucose 5.6-6.9 mmol/L (100-125 mg/dl) or 2-h plasma glucose during OGTT 7.8-11 mmol/L (140-199 mg/dl) or • Type 2 diabetes: HbA1c >–48 mmol/mol (>–6.5%) or fasting plasma glucose >–7.0 mmol/L (>–126 mg/dl) or 2-h plasma glucose during OGTT >–11.1 mmol/L (>–200 mg/dl) or • Treatment for type 2 diabetes
Overweight/ Obesity	Body mass index •≥25 kg/m2 (≥23 kg/m2 in people of Asian ethnicity) Waist circumference • ≥94 cm in men and ≥80 cm in women (Europeans) • ≥90 cm in men and ≥80 cm in women (South Asians and Chinese) • ≥85 cm in men and ≥90 cm in women (Japanese)
Dyslipidaemia	• High tryglicerides: ≥1.7 mmol/L (>–150 mg/dl) or • Low HDL-cholesterol: <–1.0 mmol/L (<–39 mg/dl) in men and <–1.3 mmol/L (<–50 mg/dl) in women or • Lipid lowering treatment
Hypertension	• ≥130/85 mmHg or treatment for hypertension
Obstructive sleep apnoea	
Polycystic ovary syndrome	
Other Comorbid Conditions	• HIV infection • Inflammatory bowel disease
Older age	Age >50 years old
Family history of MASLD	
Hispanic population	
Menopausal status	

Table 1. Risk factors for MASLD and liver fibrosis; *courtesy of Giada Sebastiani, MD, Felice Cinque, MD*

Abbreviations: HbA1c = glycated haemoglobin; **HIV =** Human Immunodeficiency Virus; **HDL =** high-density lipoprotein; **OGTT =** oral glucose tolerance test

MASH.[15] However, it is costly, invasive, and susceptible to high sampling and inter-operator variability. Hence, several non-invasive tests have been developed demonstrating high accuracy in assessing steatosis and fibrosis, but not steatohepatitis. They can be classified in (i) imaging assessing liver's anatomy (abdominal ultrasound); (ii) methods to assess physical properties of the liver, such as stiffness and attenuation, namely controlled attenuation Parameter (CAP); transient elastography (TE); shear wave elastography (SWE); (iii) blood-based tests, such as Fibrosis-4 (FIB-4), NAFLD fibrosis score (NFS); and Enhanced Liver Fibrosis (ELF).

Due to its accessibility and cost-effectiveness, abdominal ultrasound remains the most widely used tool for first-line steatosis detection, yielding 85% sensitivity (80%-89%) and 94% specificity (87%-97%), respectively.[15] Steatotic liver exhibits increased brightness and echogenicity on ultrasound compared to normal liver tissue and the right kidney (hepatorenal contrast). However, ultrasound can only detect steatosis above 20%, is susceptible to inter-operator variability, and is challenging in obese patients.

CAP, a point-of-care technique on the Fibroscan device, quantitatively assesses liver fat by measuring the attenuation of ultrasound signals through the liver. Although no universally agreed-upon thresholds exist, values above 275 dB/m demonstrate over 90% sensitivity in detecting steatosis.[15]

TE by Fibroscan employs a low-frequency vibration to generate shear waves in liver tissue measuring their velocity to determine liver stiffness, which represents a quantitative measure of liver tissue rigidity and serves as a surrogate for liver fibrosis. Widely used and validated, thresholds of 8 kPa to rule out and 12-15 kPa to rule in advanced fibrosis are currently recommended.[15]

SWE is a tool similar to TE that employs focused ultrasound beams to generate shear waves within the liver tissue. Meta-analyses indicate comparable performance to TE in measuring liver stiffness. Despite this, it sees less frequent use in hepatology clinics, and there is limited data available for MASLD patients.

Several serum markers and scores have been developed to assess liver fibrosis, with FIB-4 (based on AST, ALT, age, and platelets) and NFS (based on age, BMI, AST/ALT ratio, platelets, hyperglycemia, and albumin) being the most validated. FIB-4< 1.3 and NFS< -1.455 rule out advanced fibrosis, while FIB-4>2.67 and NFS>0.676 rule in advanced fibrosis.[15] These scores, quickly calculated from simple

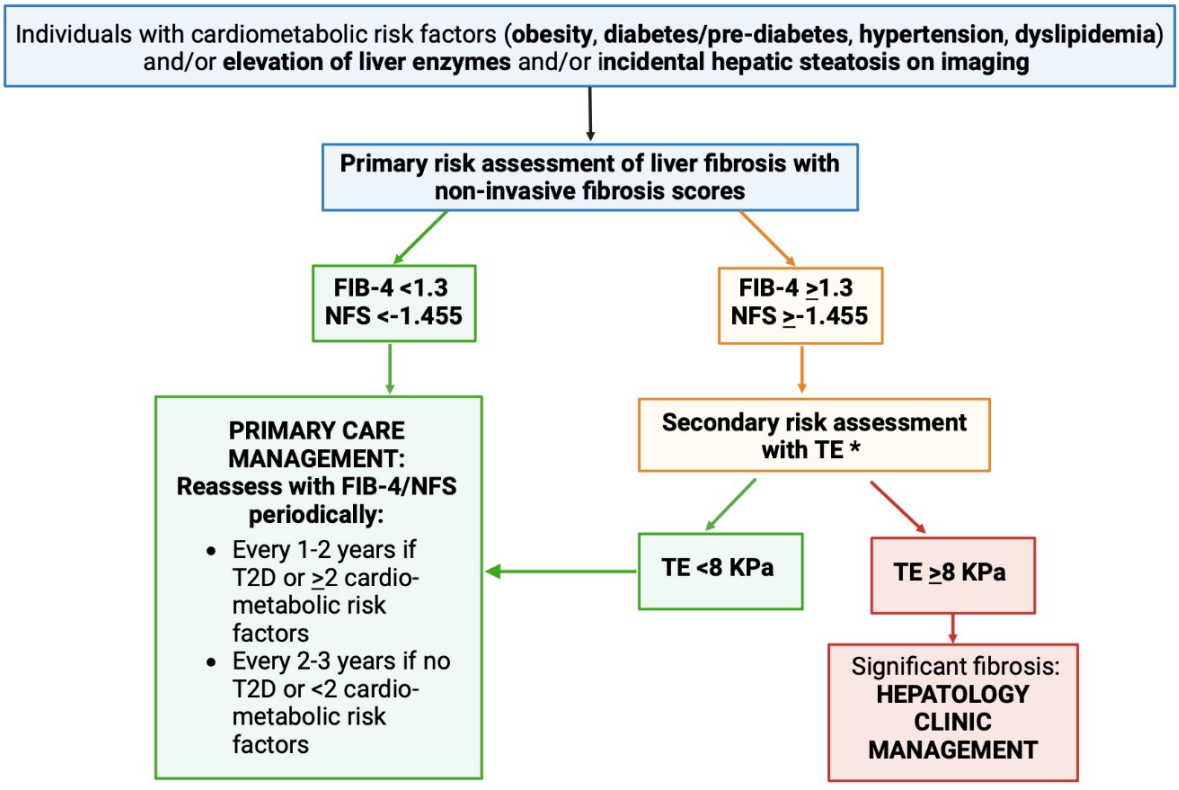

Figure 2. Algorithm for liver fibrosis assessment of patients at risk for or with established MASLD in primary care; *courtesy of Giada Sebastiani, MD, Felice Cinque, MD*

* The Enhanced Liver Fibrosis (ELF) test, with a cut-off of less than 7.7, can be used as a second-line test in lieu of transient elastography to rule out significant liver fibrosis, particularly in rural or remote areas with limited access to transient elastography.

Abbreviations: CAP = controlled attenuation parameter; **FIB-4 =** fibrosis score; **MASLD =** metabolic dysfunction associated steatotic liver disease; **TE =** transient elastography.

variables readily available in primary care, are easily repeatable. However, approximately one-third of patients receive an undetermined result, falling between the upper and lower cut-off values, necessitating additional tests to confirm liver fibrosis. Consequently, they play a role primarily in population screening, aiding physicians in identifying patients within primary care who need referral to hepatology clinics.[15] Patented serum fibrosis biomarkers have also been developed, such as ELF, which is a combination of three biomarkers (hyaluronic acid, tissue inhibitor of metalloproteinases 1, and amino-terminal propeptide of type III collagen) and is recommended in current guidelines as a second-tier test to assess advanced fibrosis.[5]

Screening and Management of MASLD and Related Fibrosis in Primary Care

In primary care, individuals with T2DM or other cardiometabolic risk factors, and/or elevated transaminases, and/or incidental hepatic steatosis on imaging are highly suspicious for MASLD and at risk for developing liver fibrosis, which is the major prognostic factor predicting hepatic and extrahepatic complications, including all-cause mortality, in MASLD.[16] Therefore, these patients require initial testing to rule out advanced liver fibrosis with non-invasive scores, with FIB-4 considered the best performing simple score according to major guidelines (**Figure 2**).[5] This approach optimizes resource use by identifying high-risk patients needing hepatology care and avoiding unnecessary referrals for those with simple steatosis, manageable by primary care physicians. Two points need to be emphasized. First, T2DM is the greatest risk factor for liver fibrosis, with MASLD and T2DM creating a perfect storm that increases the risk of cirrhosis and HCC. Indeed, international hepatology and diabetology guidelines recommend screening people with T2DM for MASLD-related liver fibrosis.[5,17] Second, nearly 80% of MASLD patients have normal transaminase levels, including 20% of those with MASH and 15% with advanced fibrosis.[5] While elevated liver enzymes are a red flag for MASLD and liver fibrosis, reliance on transaminase levels alone is inadequate, and at-risk patients should be screened for liver fibrosis even if their transaminase levels are normal. Current guidelines suggest that FIB-4 or other non-invasive scores should be used periodically to monitor patients at risk for liver fibrosis. Given the high negative predictive value of FIB-4 in ruling out advanced fibrosis, patients with a negative result (FIB-4 <1.3) can be followed up in primary care and undergo a repeat risk assessment every two to three years. Patients with T2DM or two or more cardio-metabolic risk factors should undergo FIB-4 reassessment more closely, at least every one to two years, given the higher risk of MASLD progression. Individuals with an indeterminate (1.3< FIB-4 > 2.67) or positive (FIB-4>2.67) result require secondary risk assessment to confirm advanced fibrosis with TE or ELF testing, depending on availability. MASLD patients with confirmed advanced fibrosis should be referred to hepatology care.

Implementing this stepwise screening strategy is crucial for the early detection and management of MASH and related fibrosis, allowing timely intervention on hepatic and extrahepatic complications.[5]

Current and Emerging Therapies for MASLD

While treatment options for MASLD are rapidly advancing with the FDA approval of Resmetirom, the first authorized medication for MASH, lifestyle intervention remains the cornerstone of treatment. The goal of lifestyle intervention, whether through diet, physical activity or ideally a combination of both, is to achieve a 7%-10% weight loss for overweight/obese patients and 3%-5% for lean patients.[5] The Mediterranean diet has the strongest evidence for MASH regression, but any calorie restriction strategy like the ketogenic, DASH or low-carb diets, or intermittent fasting can be recommended to improve MASLD outcomes.[18] Regardless of weight loss, diet quality is crucial. Patients with MASLD are advised to avoid refined carbohydrates, sugar-sweetened beverages, alcohol, and red meat. Instead, they should prioritize high fibres, unsaturated fats and vitamins from fruits; vegetables; legumes; nuts; olive oil; white meats; low-fat dairy; coffee; and small, controlled portions of dark chocolate.[14] Regarding physical activity, patients should aim for at least 150-300 minutes of moderate intensity aerobic exercise or 75-150 minutes of vigorous intensity aerobic exercise weekly, divided into three to five sessions.[19] Adding two days per week of muscle-strengthening activity provides additional benefits. Patients should start with small amounts of exercise, gradually increasing frequency and intensity, and minimize sedentary behaviour.[19] Bariatric surgery is a proven option for morbidly obese patients with MASLD, as evidence suggests that it not only improves MASH, but also cardiovascular outcomes.[5] Effectively managing metabolic comorbidities with appropriate pharmacotherapy for hypertension, dyslipidemia, and T2DM, is crucial in MASLD, contributing to mortality reduction.[5] For patients with MASLD at risk of adverse outcomes, including those with MASH, significant fibrosis ≥ F2, or high risk of rapid disease progression (e.g., with T2D, metabolic syndrome, persistently increased transaminases, high necroinflammation), MASH-targeting drugs may be considered.[5] Following promising results from the phase 3 MAESTRO-NASH trial[20], resmetirom - an oral, liver-targeted, selective thyroid hormone receptor agonist - became the first FDA-approved drug for treating MASH with F2-F3 fibrosis. Additionally, current guidelines recommend vitamin E and pioglitazone, approved for other metabolic conditions, as effective treatments for MASH in the appropriate clinical settings.[5] Vitamin E 800 UI daily is recommended as a short-term therapeutic

option for non-diabetic MASH patients. Pioglitazone, approved for T2DM treatment, showed promising results on MASH and cardiovascular outcomes and might be recommended in individuals with T2DM and fibrotic MASH. Interestingly, other antidiabetic drugs, namely the glucagon-like peptide-1 receptor agonists semaglutide and tirzepatide, have shown promising effects on MASLD in phase 3 trials. Current guidelines suggest considering semaglutide for treating obesity and T2DM in patients with MASH, although its anti-fibrotic effects have not yet been proven.[5]

Conclusion

MASLD is a significant global health challenge and needs to be addressed appropriately in the primary care setting. Individuals with cardio-metabolic factors, and in particular T2DM, transaminases elevation or incidental hepatic steatosis on imaging should undergo initial non-invasive assessment for liver fibrosis (FIB-4, NFS). This will help identify patients with suspected advanced fibrosis for further testing and referral to the hepatology clinic. The FDA-approval of resmetirom and ongoing research into new therapies offer hope for the future of MASLD management, although lifestyle interventions remain essential.

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