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INSIDE THIS EDITION:

Chronic Cough

Pathophysiology: The Hepatobiliary System

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Chronic Cough in Adults

Includes 5 Advanced Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses, physicians, and physician assistants/associates involved in the care of patients with chronic cough.

Course Objective
Chronic cough is difficult to effectively assess and treat, leading to extended periods before diagnosis and significant negative impact on patients' quality of life. The purpose of this course is to provide clinicians with the knowledge and skills necessary to identify and treat patients with chronic cough, regardless of underlying etiology, in accordance with clinical guidelines.

Learning Objectives
Upon completion of this course, you should be able to:

1. Describe the background and terminology related to chronic cough.
2. Compare and contrast available cough severity measures.
3. Outline the epidemiology of chronic cough and underlying etiologies.
4. Evaluate the impact of chronic cough on various dimensions of patients' lives.
5. Discuss the natural history and course of chronic cough.
6. Describe the pathophysiology of chronic cough.
7. Outline components of the initial evaluation of patients with chronic cough.
8. Identify potential underlying etiologies of chronic cough as well as appropriate management approaches for these conditions.
9. Analyze available treatment modalities for chronic cough of various underlying causes, including upper respiratory, lower respiratory, and reflux-associated cough.
10. Identify appropriate modalities for the treatment of refractory chronic cough, including pharmacotherapy, nonpharmacologic approaches, and investigational agents.

Faculty
Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that

represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure
Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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INTRODUCTION

Chronic cough, or cough lasting longer than eight weeks, is a debilitating disease that can result in patients coughing hundreds to thousands of times every day. This physically exhausting and socially isolating condition can persist for years or decades, degrade the quality of life in nearly every domain, and result in numerous medical and psychosocial consequences, yet its adverse impact on patients is often overlooked or underappreciated by clinicians. While acute cough is typically transient and self-limited, chronic cough often poses a diagnostic and therapeutic challenge; both non-treatment and over-treatment with ineffective medication are common [1; 2]. Cough that persists despite investigation and treatment is especially vexing for patients and clinicians [3].

BACKGROUND

How are acute, subacute, and chronic cough defined?

The anatomic, diagnostic protocol (ADP) established in the late 1970s that chronic cough in patients with negative chest x-ray findings is a symptom of asthma, postnasal drip, or acid reflux. Later refined to asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and GERD, it was believed that treating these underlying etiologies led to a favorable outcome in 90% of patients with chronic cough [4; 5; 6].

However, a large proportion of patients with these conditions do not have chronic cough [7]. Moreover, in many patients, cough persists despite treatment of its presumed cause (referred to as refractory chronic cough) or an underlying cause cannot be identified (referred to as unexplained chronic cough) [8]. This suggested that additional pathophysiological processes were involved [7].

In 2014, the European Respiratory Society (ERS) introduced cough hypersensitivity syndrome, defining chronic cough as a distinct clinical entity [9]. The 2020 ERS clinical practice guideline for chronic cough was pivotal in establishing cough hypersensitivity syndrome, influencing subsequent national and international chronic cough guidelines [10; 11; 12; 13].

In 2016, the "treatable traits approach" was introduced to improve the outcomes of pulmonary patients with complex clinical syndromes (e.g., asthma and COPD) and variable treatment responses by moving beyond practice guidelines directed at diagnostic categories as a single disease entity, to identify and treat relevant phenotypic and endotypic "traits" instead [14; 15; 16]. The treatable traits approach gained rapid acceptance in pulmonary medicine and endorsement in chronic cough guidelines [5; 17; 18].

Cough performs an essential physiological function, mediated by cough reflex pathways in the airways and brain. In some individuals, irritation or inflammation of vagal afferent nerves in the airway leads to cough reflex hypersensitivity, the cardinal feature of cough hypersensitivity syndrome, peripheral and central sensitization, and clinical manifestations of allotussia, hypertussia, and/or laryngeal paresthesia (***Table 1***) [3; 19; 20]. The demographic, pathophysiological, and clinical similarities between cough hypersensitivity syndrome and chronic neuropathic pain are numerous. Chronic pain research has substantially informed how chronic cough and cough hypersensitivity syndrome are understood; both are disorders of sensory processing [4; 21; 22].

Sensitization of cough pathways may persist long after resolution of the inciting acute or subacute event. These chronic coughs will remain unexplained by diagnostic workups that do not consider cough hypersensitivity. Cough hypersensitivity syndrome may improve with the targeted intervention of other treatable traits. If chronic cough persists, the patient has refractory chronic cough [5].

Refractory and unexplained chronic cough are diagnoses of exclusion. A thorough, systematic clinical workup is required so that non-obvious and obvious causes of chronic coughing can be identified. The treatable traits approach may significantly expand clinically important intervention targets. After a diagnosis of refractory/unexplained chronic cough is made, therapeutic attention shifts to downregulating the hypersensitive cough reflex [5].

Maturation in research and practice has led to novel and emerging therapeutic options for patients with refractory chronic cough. Randomized controlled trials of existing centrally acting agents have identified the efficacy of low-dose morphine and gabapentin [10; 23; 24]. The development of P2X3 receptor antagonists, a novel peripherally acting drug class, has led to the approval of gefapixant for the treatment of refractory chronic cough in the European Union, Japan, and Switzerland, with U.S. Food and Drug Administration (FDA) advisory committee review believed imminent as of 2024 [25]. In a given patient, refractory/unexplained chronic cough may primarily involve peripheral mechanisms, central mechanisms, or both, and no tool is available for predicting therapeutic response to peripherally or centrally acting antitussive agents.

As of 2024, there are no FDA-approved treatments for chronic cough or for refractory chronic cough. When chronic cough persists after potential underlying causes are identified and treated according to current practice guidelines (e.g., for chronic cough related to nonasthmatic eosinophilic bronchitis or GERD), all therapeutic options for refractory chronic cough are prescribed off-label.

CHRONIC COUGH TERMINOLOGY	
Term	**Definition**
Acute cough	Cough lasting less than 3 weeks
Subacute cough	Cough lasting 3 to 8 weeks
Chronic cough	Cough lasting more than 8 weeks
Refractory chronic cough	Cough that persists despite guideline-based treatment of the presumed underlying cause(s)
Unexplained chronic cough	No diagnosable cause of cough is found despite extensive investigation for common and uncommon causes
Allotussia	Cough triggered by innocuous stimuli (e.g., laughing, talking, changes in ambient temperature)
Hypertussia	Exaggerated coughing triggered by mildly tussive stimuli (e.g., strong odors, second-hand cigarette smoke)
Urge to cough (laryngeal paresthesia)	A distinct, often debilitating sensation of irritation or "itch" in the throat or chest that precede cough and is not satiated by coughing
Cough reflex hypersensitivity	The cardinal feature of cough hypersensitivity syndrome
Cough hypersensitivity syndrome	Disorder characterized by cough triggered by mildly tussive or innocuous stimuli, with features of allotussia, hypertussia, and/or laryngeal paresthesia
Source: [5; 9; 26]	*Table 1*

Important knowledge advances in this rapidly evolving field are not reaching healthcare professionals in the United States because chronic cough guidelines published for domestic consumption have become outdated. From this course, clinicians will gain current information on chronic cough and refractory/unexplained chronic cough, including the pathophysiology, differential diagnosis, and clinical management, essential for healthcare professionals in primary care, respiratory medicine, and ear/nose/throat (ENT) settings.

COUGH SEVERITY MEASURES

What benefits do patient-reported outcome measures have over objective measures?

Patients with chronic cough experience cough-related physical, psychological, and social burdens, which can result from different aspects of cough severity, including cough frequency, cough intensity, disruption of daily activities due to cough, and cough-specific health-related quality of life. The severity and impact of chronic cough on physical, psychological, and social domains can be quantified through several validated objective and subjective measures [27].

Patient-reported outcome measures obtain a comprehensive understanding of the impact across these domains [27]. Patient-reported outcomes capture many issues that cannot be assessed effectively by objective measures and are also inexpensive, readily available, convenient, and easy to use for the patient [28]. A minimal clinically importance difference, the smallest change in an outcome that patients would perceive as important, is established for both objective and patient-reported outcome tools [29]. Cough measures mentioned throughout this course are summarized in ***Table 2***. Cough frequencies of greater than 700 over an hour have been recorded [28].

EPIDEMIOLOGY

PREVALENCE

What is the estimated prevalence of chronic cough among U.S. adults?

Cough is a frequent reason for seeking outpatient medical attention in the United States, accounting for as many as 30 million clinical visits per year, up to 40% of which result in specialist referral [31].

Chronic cough has a prevalence among U.S. adults of roughly 10%, of whom 92% visited healthcare clinicians in the past six months [32]. Chronic cough is estimated to cost $6.8 billion annually in the United States, and an estimated $3.6 billion is spent annually on over-the-counter therapies [33]. The economic implications of chronic cough include the cost of outpatient visits, plus diagnostic workups, prescription medications to treat cough, and lost work and lost school

COUGH MEASURES		
Name	**Domains/Items, Rating and Minimal Clinically Importance Difference (MCID)**	**Comments**
Health-related quality of life patient-reported outcome tools		
Leicester Cough Questionnaire (LCQ)	Seven-point Likert scale (1=all of the time; 7=none of the time); 19 items in 3 domains: physical, psychological, and social. Total score range: 3 (maximal impairment) to 21 (no quality-of-life impairment). MCID: 1.5 to 2.5 increase	The most widely used tool for assessing quality of life impact of chronic cough
Cough Quality of Life Questionnaire (CQLQ)	Four-point Likert scale (1=strongly disagree; 4=strongly agree); 28 items over 6 domains: physical and extreme physical complaints, psychosocial issues, emotional well-being, safety fears, and functional abilities. Total score range: 28 (no adverse effect of cough) to 112 (worst possible impact). MCID: 10.6 to 21.9	Contains more items on physical impact of chronic cough (e.g., fractured ribs, headaches, immune deficiency, tuberculosis)
Hull Airway Reflux Questionnaire (HARQ)	Six-point scale (0=no symptoms; 5=most severe) of 14 items that measure airway hypersensitivity in chronic cough. Total score range: 0 to 70 Normal is <14 MCID: 16	Also used as a diagnostic tool for airway reflux, and to assess unexplained respiratory symptoms
Cough Severity Diary (CSD)	11-point scale (0=never; 10=constantly) of 7 items on frequency; intensity; disruptiveness MCID ≥1.3 total score, −1.4 to −1.1 domain scores	Captures the severity and impact of chronic cough. Developed in response to patient feedback.
Objective assessment tools		
VitaloJAK Cough monitor Leicester Cough Monitor (LCM)	Electronic cough recording monitors worn by patients to measure cough frequency, typically as coughs per hour over 24 hours MCID: ≥20% to 30% decrease	Does not capture the episodic nature of chronic cough, a primary factor in patients' disease burden
Subjective tools		
Visual Analogue Scale (VAS)	Score range 0 (no cough) to 100 mm (worst cough ever) MCID: 30-mm reduction on the 100-mm cough severity VAS	—
Numerical Rating Scale (NRS)	Score range 0 (no cough) to 10 (worst cough ever)	

Source: [28; 29; 30] *Table 2*

productivity [1]. While inconsistent definitions prohibit direct comparisons of chronic cough prevalence between different countries or ethnicities, chronic cough appears to be more common in Europe, North America, and Australia than in Asian countries [32; 34].

In KNHANES, a nationally representative study of the Korean adult population, the point prevalence of acute (<3 weeks), subacute (3 to 8 weeks), and chronic (>8 weeks) cough was 2.5%, 0.8% and 2.6%, respectively. The modal durations of current cough were less than one week (31.1%), and more than one year (27.7%); this bimodal distribution reflects the different pathophysiology of acute and chronic cough [35].

REFRACTORY AND UNEXPLAINED CHRONIC COUGH

Refractory chronic cough is seen in 20% to 59% of patients presenting to specialist cough clinics [36]. At Kaiser Permanente Southern California, 11,290 patients with specialist-diagnosed chronic cough were treated and followed for one year; 40.6% continued coughing despite etiological treatment by specialists (i.e., refractory chronic cough) [37].

Roughly 10% of patients with chronic cough lack an identifiable cause despite thorough evaluation (i.e., unexplained chronic cough), including 17% of patients with chronic cough in the Kaiser Permanente cohort [1; 37]. Of 43,453 patients receiving primary care for chronic cough in the UK, 31% had ongoing chronic cough in the absence of associated comorbidities (i.e., no causal explanation or unexplained chronic cough) [4].

DISEASE BURDEN AND HEALTHCARE UTILIZATION

The Kaiser Permanente study examined the disease burden of chronic cough in comorbidities, medication use, and exacerbations [37]. Diagnoses included GERD (44%), hypertension (42%), allergic rhinitis (33%), chronic rhinitis (31.5%), asthma (31%), chronic sinusitis (24.4%), obesity (24%), upper airway cough syndrome (20.4%), depression (20%), and cough complications (19%). Nearly 40% of patients with unexplained chronic cough consulted at least two different specialist departments. In the previous three years, about half of the patients with emergency department visits (28.5%) or hospitalizations (10%) were for respiratory events [37]. Medications were respiratory: nasal corticosteroids (55%), short-acting b2-agonists (50.5%), inhaled corticosteroids long-acting b2-agonist (27%), inhaled corticosteroid monotherapy (24%), and leukotriene modifiers (18.6%); non-respiratory: antitussive codeine (59%), proton pump inhibitors (PPIs) (45%), antidepressants (26%), anxiolytics (15.5%), and gabapentinoids (14%); and other: systemic antibiotics (72.4%) and oral corticosteroids (47%).

Over one year, patients with emergency department visits (26%) and hospitalizations (12%) remained high; more than 50% were respiratory-related. Antitussive and psychotherapeutic drugs were dispensed at a frequency similar to the baseline year. The clinical and economic burden was especially high in patients with both respiratory disease and GERD, but chronic cough persistence (40.6%) was similar between subgroups [37].

A subsequent Kaiser Permanente study of patient-level burden used patient-related outcomes (average chronic cough 8 years) [38]. Mean scores were 11 on LCQ (maximum: 21), 33 on HARQ (normal: ≤13), and 57 on CQLQ (maximum: 112). Correlations were high between LCQ and HARQ (–0.65), LCQ and CQLQ (–0.80), and HARQ and CQLQ (0.69). Patients with chronic cough-related respiratory and gastrointestinal disorders were generally similar. Treatment responses were suboptimal. Women (compared with men) and non-White individuals (compared with White individuals) reported significantly worse cough severity and poorer LCQ, HARQ, and CQLQ scores.

The patient-reported burden of chronic cough was substantial, with long duration, high severity, poor health status, high degree of cough hypersensitivity, low quality of life, multiple cough triggers, and frequent laboratory testing, specialist care, and medications. The study provides strong evidence that patients with chronic cough exhibit frequent poor responses to medications and overall control [38].

The objective and patient-reported burden of chronic cough is substantial, particularly in women and non-White minorities, which markedly affects daily living with inadequate response to treatments.

RISK FACTORS

Risk factors of chronic cough include smoking, female sex, older age, obesity, asthma, allergic rhinitis, rhinosinusitis, and angiotensin-converting enzyme (ACE) inhibitor use for hypertension treatment [34; 39].

In the United States, 18% of adults who smoke cigarettes have chronic coughs [39]. Cigarette smokers are three times more likely to report chronic cough than never-smokers and ex-smokers, and the cough is usually due to chronic bronchitis. However, most patients in cough specialist clinics are nonsmokers [19]. Among 1,000 patients evaluated at a cough center in the Bronx, 2.7% were active smokers and 27% former smokers [40]. Of 11,290 Kaiser Permanente patients with chronic cough, 65% were never-smokers and 2.3% were current smokers [37].

Age and sex underlie the burden and prevalence of chronic cough; more than 67% of patients presenting with chronic cough to specialist clinics are female, likely due to gender differences in cough reflex sensitivity [1; 19]. Cough reflex sensitivity was assessed in individuals from China, India, and northwest Europe. No differences between ethnic groups were found, suggesting that racial variation in chronic cough prevalence may not reflect differences in cough reflex sensitivity and may be influenced by asthma, allergy, or environmental factors [34; 39; 41]. Women in all three ethnic groups demonstrated lower cough thresholds [41].

While chronic cough can occur at any age, the rate rises substantially in women who are 40 years of age or older and is highest in the 60 to 69 age group. The highest rates in men occur between 50 and 69 years of age [1]. In KNHANES, chronic cough increased significantly with age. The odds ratio of 2.20 suggests a substantial increase in chronic cough likelihood for individuals 65 years of age or older (compared with those 18 to 39 years of age). The associations with older age were independent of current smoking and comorbidities [35].

In separate longitudinal European population studies, chronic cough was associated with low educational level and lower socioeconomic status [34]. A systematic review found a significant association between low education level and risk of chronic cough [42].

In South Korea and China, higher male prevalence of chronic cough was attributed to differences in smoking habits and air pollution exposures, respectively [28]. Occupational irritants, such as fumes, gases, cleaning products or dust, may cause cough by triggering cough reflex or by inducing oxidative stress and eosinophilic inflammation, but the effect of such factors on chronic cough remains elusive. Air pollution is an important risk factor for chronic cough. Levels of fine particulate matter ≤2.5 mcm in diameter (or PM2.5) are higher in East Asian than in European or North American countries but the prevalence of chronic cough is lower, suggesting potential host-environment interactions in developing chronic cough [19].

Persistent cough is a class-wide adverse effect of ACE inhibitors, and the 5% to 35% prevalence is much higher in East Asian than in other populations. In genotype studies, the genetic polymorphisms ACE I/D and SLCO1B1 were related to ACE inhibitor-induced cough and were more common in East Asian populations, which may account for the ethnic differences and possibly predict risk of ACE inhibitor-induced cough [43].

PATIENT IMPACT OF CHRONIC COUGH

Patients report numerous cough-related physical and psychosocial effects, most commonly fatigue, sleep disturbance, exhaustion, breathlessness, headache, dizziness, musculoskeletal pain, wheezing, impairment of speech, vomiting, excessive perspiration, self-consciousness, and interference with daily activities [28; 44]. These effects have a significant impact on patients' quality of life.

PHYSICAL IMPACT

What physical complications are associated with chronic cough?

During vigorous coughing, intrathoracic pressures may reach 300 mm Hg and expiratory velocities approach 500 miles per hour (mph) (85% of the speed of sound). These physical forces cause many of the cardiovascular, gastrointestinal, genitourinary, quality of life, musculoskeletal, neurologic, ophthalmologic, psychosocial, and respiratory complications of chronic cough, ranging from the relatively minor to life-threatening or even fatal. Comorbid illnesses or older age can magnify these effects [44; 45].

Surgical Complications and Hernia

Surgical complications from uncontrolled coughing include extrusion (i.e., expulsion) of ocular contents during eye surgery, and wound dehiscence (i.e., splitting or bursting open) following cardiac or abdominal surgery. Similarly, severe coughing can cause inguinal, femoral, umbilical, lumbar, or abdominal wall hernia [45].

Fracture

Cough-induced rib fractures, another painful and potentially serious complication of chronic cough, often involve multiple ribs, particularly ribs 5 through 7. The number of ribs fractured is associated with higher mortality rates, particularly in older patients who often have decreased bone density due to osteoporosis (also an adverse effect of long-term corticosteroid treatment). However, rib fractures can also occur in patients with normal bone density [44; 46].

Stress Urinary Incontinence

Stress urinary incontinence, defined as the unintentional loss of urine during or following a bout of coughing or other physical activity, significantly contributes to quality-of-life disruption caused by chronic cough in women. Of 210 consecutive adult women evaluated at a cough center for chronic cough, 63.3% reported stress urinary incontinence induced by cough episodes; stress urinary incontinence developed after the onset of chronic cough and solely occurred during or after coughing in 92.5% and at least daily in 47.3%. For context, 3.5% of similarly aged women in the community experience stress urinary incontinence, while only 5% of men with chronic cough report stress urinary incontinence as an issue significantly impacting their quality of life [28; 47].

Surveys have reported lower rates of urinary incontinence in women with chronic cough, but most women will not volunteer a history of cough-induced stress urinary incontinence unless specifically asked. This may explain the higher prevalence in this study, because the establishment of trust between patient and physician may have encouraged sharing such information. After discussion ensues, patients are often relieved to learn this is a common problem faced by women with chronic cough [47].

Cough Syncope

Cough-evoked syncope is a serious and potentially fatal consequence of coughing. Numerous reports of motor vehicle accidents resulting from cough syncope include the deaths of drivers and pedestrians. While the exact mechanism of remains debated, the required generation of very high intrathoracic pressures likely explains the nearly uniform profile of patients with cough syncope as large male subjects with obstructive airway disease [48]. Cough syncope is considered relatively uncommon, although 10% of subjects with chronic cough in a community sample reported experiencing cough syncope [5; 49]. The mandatory loss of driver's license in some countries (e.g., the UK) has a major impact on employment prospects for these patients [28].

PSYCHOSOCIAL AND QUALITY OF LIFE IMPACT

Chronic cough can interfere with all aspects of patients' lives, including daily living activities, social interactions, home management, recreational activities, and employment. Importantly, when triggers of coughing bouts are very difficult to avoid, the psychosocial impact can be substantial. Chronic cough has a negative impact on relationships, with spouses not being able to tolerate the cough as a key reason for patients' health-related dysfunction [28]. In a multinational European survey of 1,120 persons with chronic cough, most reported that coughing affected their quality of life (96%), disturbed their family and friends (94%), and affected activities they enjoyed (81%) [51].

The psychological effects associated with chronic cough are highly prevalent, with an impact on mental health comparable to that of stroke or Parkinson disease. Studies of patients with chronic cough have reported high rates of anxiety (33% to 52%) and depression (16% to 91%) [28].

Patients may avoid or be uncomfortable in social situations due to the embarrassment of coughing, its effects (e.g., stress urinary incontinence, retching), and/or the perception by others that they have a contagious condition or are a heavy smoker [28]. The COVID-19 pandemic increased the social stigma of persistent coughing due to its association with contagious respiratory diseases [50].

NATURAL HISTORY AND DISEASE COURSE

What FEV1 findings are common in adult patients with chronic cough?

Little is known about the natural history of cough hypersensitivity, but the available evidence suggests that patients often suffer from it for many years [4]. In a longitudinal study of patients with unexplained chronic cough, cough severity worsened (36%) or was unchanged (23%) over 7 to 10 years. Predictors of cough persistence or improvement could not be identified. Unexpectedly, longitudinal spirometry data showed declines in forced expiratory volumes over one second (FEV1) that were well above population norms for similarly aged nonsmokers. The striking magnitude of decline argued against a chance finding. Around 10% of patients developed spirometric features of COPD [52].

The abnormally rapid decline in FEV1 and a significant minority of patients developing COPD raise the possibility that unexplained chronic cough is associated with a persistent damaging airway process and could be a risk factor for COPD [52]. A 2023 study confirmed that chronic cough is highly associated with FEV1 decline, regardless of COPD presence, while chronic cough in patients suffering from COPD is associated with lower FEV1, more dyspnea, worse health status, and is an independent risk factor for exacerbations of COPD possibly linked to altered transient receptor potential (TRP) channel function [53].

Cough is often the most bothersome and intractable symptom reported by patients with asthma, and the significant disease burden of chronic cough was described in a prospective cohort of 323 consecutive adult participants with asthma who received optimized asthma therapy. After 12 months, those with chronic cough had more airflow obstruction; worse asthma control and quality of life; increased airway inflammation; upper respiratory tract infection as a trigger; more psychological, rhinitis, and COPD comorbidities; greater work productivity loss and daily activity impairment; and increased exacerbations. These findings call for more attention to chronic cough in asthma [54].

In summary, chronic cough is related to an accelerated FEV1 decline over time, regardless of smoking history or COPD diagnosis, but the relationship between chronic cough and worse clinical outcomes lacks a clear pathophysiological explanation [55].

PATHOPHYSIOLOGY OF CHRONIC COUGH

NORMAL PHYSIOLOGY

The Cough Reflex

Cough is an innate reflex that protects the airways from foreign objects, clears excess secretions, and preserves airway patency. The cough reflex consists of peripheral airway receptors of afferent nerves, cough control centers in the central nervous system (CNS), and efferent nerves.

Cough occurs in three phases [31; 56]. The first is inspiratory, during which the glottis opens widely followed by rapid inhalation sufficient for generating enough air movement to be productive. The second phase is compression. This phase is characterized by the rapid closure of the glottic apparatus and contraction of abdominal and other respiratory muscles compresses the alveoli and bronchiole, increasing intrathoracic pressure to greater than 300 mm Hg. The final phase is expiration, or the sudden opening of the epiglottis and vocal cords results in rapid, high-volume expiratory airflow that may exceed 500 mph in velocity. The force of this process loosens and expels mucous secretions from the airway wall, while the rapid airflow vibrates the larynx and pharynx, inducing the characteristic sounds of cough.

Vagal Afferents

The cough reflex is activated by vagal afferent A-δ and C fibers, sensory neurons originating from brainstem vagal ganglia that innervate the larynx and proximal airways. A-δ fibers are mechanoreceptors, activated by airway mucus, inhaled foreign bodies, and low pH (i.e., acidity). C-fibers are nociceptive chemoreceptors, activated by signaling molecules and mediators of inflammation or tissue damage within the airway [19; 25; 57; 58].

Neurobiological Processes

Complex neurobiological processes in the peripheral nervous system, brainstem, and higher cerebral cortex mediate coughing [59]. Receptors (e.g., P2X3 purinergic receptors, voltage-gated sodium channels [NaV], bradykinin receptors, and transient receptor potential [TRP] ion channels) and neuropeptides (e.g., substance P, calcitonin gene-related peptide [CGRP]) play important roles [60].

Noxious mechanochemical stimuli in the airways activate ligand-gated ion channels and G protein-coupled receptors on vagal nerve endings; NaV channels depolarize, propagating the signal up the vagus nerve to first-order synapses in brainstem nuclei. From there, the signal is relayed by second-order neurons to brainstem and spinal motor neurons to reflexively modify breathing; to third-order neurons of the primary somatosensory cortex where the unpleasant urge-to-cough sensation is mediated; and to higher-order cortical neurons that mediate conscious perception of cough [23; 60].

These ascending third-order pathways enable perception of airway irritation, and regulatory control of descending motor pathways that terminate in the brainstem and in spinal respiratory circuits [22; 61]. Under physiologic conditions, higher inhibitory brain processes permit the modification of coughing behavior, and the urge to cough may be suppressed [21].

Extrapulmonary airways (i.e., larynx, trachea, and mainstem bronchi) are also reflexogenic sites essential for preventing aspiration, inhalation of noxious chemicals, and accumulation of excessive mucus; all can induce reflex coughing with irritation of vagal afferent nerves [21].

Coughing is a reflex and a voluntary behavior with or without the sensation of an urge to cough. Reflex cough, behavioral cough, and the urge to cough (which precedes the motor act of coughing) are three separate entities, each dependent on their own neural processes [21; 22]. The relevance of these neurophysiological processes is apparent when considering the development of cough hypersensitivity syndrome [21].

PATHOPHYSIOLOGY OF CHRONIC COUGH AND COUGH REFLEX HYPERSENSITIVITY

Chronic cough, unlike protective cough, is a pathologic state that no longer serves a physiologic role [60]. Excessive coughing is a consequence of increased activation of neuronal cough-mediating pathways due to [62; 63]:

- Excessive activation of airway vagal afferent terminals by chemical or mechanical irritants
- Neuroplastic changes in vagal afferent fibers
- Neuroplastic changes in the CNS

Nervous system plasticity, or malleability, dictates that excessive stimulation of peripheral nerve fibers can reshape their excitability through changes in receptor expression; synaptic transmission in the CNS is subsequently altered, further increasing the gain within the system [62].

Chronic cough is most associated with and traditionally considered a symptomatic byproduct of asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and/or GERD, but most patients with these chronic inflammatory diseases do not have chronic cough. Further, cough severity correlates poorly with cough-associated disease severity, and chronic cough can occur in the absence of these conditions as unexplained chronic cough or unexplained chronic cough [19; 20; 64]. This implies individual differences in cough reflex sensitivity and that hypersensitivity of airway sensory nerves may underlie chronic cough [65].

Cough hypersensitivity, defined as repeated episodes of coughing often in response to minimal or no discernible triggers, is common to all persons with chronic cough [66]. Extracellular adenosine triphosphate (ATP) may play a prominent role in cough hypersensitivity. During cellular injury or inflammation, cells release ATP to alert neighboring cells to damage. In respiratory conditions associated with chronic cough and airway inflammation, such as COPD and asthma, extracellular ATP may be elevated and sensitivity to ATP is heightened [33]. The NK-1 receptor and its ligand, substance P, may also be involved in inducing and maintaining cough hypersensitivity, both peripherally and centrally, either indirectly through inflammatory mediators or directly by stimulating sensory nerve fibers [33].

Cough Hypersensitivity Syndrome

What is the cardinal feature of cough hypersensitivity syndrome?

Cough hypersensitivity syndrome frames chronic cough as a hypersensitivity disorder, akin to chronic pain. Sensitization of vagal afferents by upper or lower airway inflammation leads to increased cough sensitivity to normally anodyne stimuli, the cardinal feature of cough hypersensitivity syndrome [22; 58].

In chronic cough, as in chronic pain, peripheral sensitization is necessary but probably insufficient without central sensitization, which alters the efficacy of neurotransmission in the brainstem and regulation of cough reflex-mediating brain pathways [21]. Patients with cough hypersensitivity or chronic pain have shown abnormal activity in the same midbrain areas that amplify incoming cough (or pain) signals [58; 67; 68].

Chronic pain research substantially informs the conceptual transformation in how chronic cough and refractory chronic cough are understood. Both disorders involve abnormal sensory processing. Taking inspiration from chronic pain, hypertussia describes abnormal excessive coughing in response to airway irritation. Allotussia describes coughing in response to innocuous stimuli. Laryngeal paresthesia describes noxious sensations in the throat or chest associated with an "urge to cough." Peripheral and central sensitization describe processes that alter cough pathway function [62; 63].

Peripheral Sensitization

Dysregulation of airway innervation contributes to chronic coughing and is considered the main driver of cough in refractory chronic cough [63].

In airway inflammation, vagal neuron sensitization and plasticity is shown by increased production of neuropeptides, upregulation of glutamate receptors and nociceptive ion channels (e.g., TRPV1), and lower thresholds for activating sensory-evoked cough responses. Neuropeptide upregulation occurs in airway sensory neurons where they are not normally expressed. These effects underlie hypertussia by expanding the cough-evoking stimuli field [21].

For example, bronchoscopic biopsies of patients with chronic cough demonstrated increases in airway epithelial nerve length and branching. The remodeling of these vagal C fibers may contribute to airway hypersensitivity through increased density of fiber terminals and enlargement of their receptive fields. The shearing forces of chronically coughing and/or the resultant release of inflammatory mediators (e.g., ATP) may explain the increased density of epithelial innervation [69].

Whether the primary stimulus for peripheral sensitization is cellular damage, mechanical stress, or nociceptor stimulation is unclear, as all three can trigger ATP release, activating P2X3 receptors [59].

Central Mechanisms

While peripheral nervous system dysfunction is the most-described component of cough hypersensitivity, central dysfunction plays a fundamental role [70]. Patients with cough hypersensitivity attempting to voluntarily suppress coughing show reduced activity in dorsomedial prefrontal and anterior mid-cingulate cortices, suggesting diminished ability to inhibit cough reflex activation [66; 67; 71].

Patients with refractory chronic cough demonstrate structural and functional alterations in the left frontal brain regions, including lower gray matter volume and enhanced frontoparietal functional connectivity, which may underlie the higher cough scores, greater psychosocial impact, longer disease duration, and impaired cough inhibition in these patients [72].

Studies of chronic cough in asthma and nonasthmatic eosinophilic bronchitis identified increased neuronal sensitivity and subsequent central sensitization via mechanisms of inflammatory-mediated nociceptor sensitization and altered afferent nerve terminal excitability, phenotypic changes in vagal afferent neurons, and central neuroplasticity resulting from increased synaptic signaling from peripheral afferents [73].

The contribution of CNS mechanisms accounts for the efficacy of centrally acting medications (e.g., gabapentin and low-dose morphine) in patients with refractory chronic cough [58].

Laryngeal Hypersensitivity

A study of refractory/unexplained chronic cough patients with cough hypersensitivity referred to a cough clinic suggests highly prevalent laryngeal dysfunction. The 12-month cohort of all referred patients showed high rates of cough hypersensitivity (100%), multiple cough triggers (75%), laryngeal paresthesias (95%), voice abnormalities (50%), upper airway dyspnea (25%), and laryngeal functional abnormalities on nasoendoscopy (73%). Given the frequent constellation of symptoms typifying laryngeal dysfunction and cough hypersensitivity, the authors suggest designating laryngeal hypersensitivity as a specific cough phenotype [74].

Many refractory chronic cough cases have a sensory neuropathic etiology in the hypopharynx and larynx, with laryngeal hypersensitivity a key mechanism [75]. Pharyngeal/laryngeal sensations (e.g., irritation, tickle, throat-clearing), frequently associated with upper airway cough syndrome and reflux cough, may represent sensory neuron dysfunction of vagal afferents in the upper airways and a phenotype of cough hypersensitivity syndrome. Dysphonia, dysphagia, dyspnea, and abnormalities of vocal fold motion on laryngoscopy may present with chronic cough as part of the pharyngeal/laryngeal nerve dysfunction seen in cough hypersensitivity syndrome [76].

Autonomic Dysregulation

There is also evidence of broader autonomic nervous system dysregulation. Compared with healthy controls, patients with chronic cough report more frequent and severe autonomic symptoms in gastrointestinal, orthostatic intolerance, bladder, and pupillomotor domains, primarily in parasympathetically mediated systems, suggesting this population may suffer from dysautonomia. Whether this results from coughing, or if both the cough and dysfunction are part of wider vagal pathology, is unclear [70].

SUMMARY

Functional changes in TRPV1, TRPA1, and P2X3 nerve channels and the development of peripheral and central sensitization are thought to turn cough from a defensive reflex into a cough hypersensitivity syndrome [77]. Hypersensitivity of the cough reflex and deterioration in central inhibition of the cough explain cough persistence [78].

Cough hypersensitivity syndrome is identified by symptoms of allotussia, hypertussia, and/or laryngeal paresthesia and may improve with the treatment of other treatable traits. If the chronic cough persists, the patient has refractory chronic cough [5].

Owing to nervous system plasticity, sensitization of cough pathways may persist long after resolution of the inciting event, such as acute viral airway infection. These chronic coughs will remain unexplained by diagnostic workups that do not consider cough hypersensitivity [5].

Currently, there are no available methods to identify susceptibility to nervous system plasticity and sensitization, objectively diagnose cough hypersensitivity syndrome, or predict treatable versus refractory chronic cough.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the European Respiratory Society, cough hypersensitivity through cell damage and inflammation underlies much of the increased cough seen in other pathologies. The different pathological processes in individual conditions contribute to the disease-specific heterogeneous etiology of cough in other lung disease.

(https://erj.ersjournals.com/content/55/1/1901136. Last accessed August 12, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

INITIAL EVALUATION OF CHRONIC COUGH

When initially encountering a patient with chronic cough, the primary task is to perform a thorough evaluation that seeks potential underlying treatable causes of chronic cough and to treat the cause(s) according to current clinical practice guidelines [99]. These patients typically undergo extensive medical workup and treatment across multiple subspecialties without improvements in their symptoms, and clinicians should try to break the often-repetitive cycle of investigations, empirical treatment, and worry experienced by these patients [75]. The degree to which patients have been investigated varies, so basic tests may be required. Further investigations depend on the individual's presentation [5]. After a diagnosis of refractory chronic cough is made, the therapeutic focus shifts from identification and treatment of underlying causes to suppression of the hypersensitive cough reflex [99].

The initial evaluation (detailed history and physical examination) accomplishes the key tasks of identifying or ruling out a wide range of diseases underlying the chronic cough and identifying any danger signs that may indicate a diagnosis that needs urgent attention. Any positive findings should guide the initial management [8; 44].

DEFINITIONS OF COUGH

To eliminate confusion on how to define cough, the American College of Chest Physicians (ACCP) and the ERS have standardized the definition of cough according to its duration [10; 100]. Consistently applying these guideline-established definitions is crucial [2].

Thus, the first step in evaluating cough is to determine its duration. This also helps to narrow the differential diagnosis based on the most common underlying causes [10; 100]:

- Acute (<3 weeks) cough:
  - Infectious etiologies, especially with viral causes
  - Exacerbations of chronic diseases (e.g., asthma, COPD)
  - Pneumonia
  - Environmental exposures
- Subacute (3 to 8 weeks) cough:
  - Postinfectious cough
  - Exacerbations of chronic diseases (e.g., asthma, COPD)
  - Upper airway cough syndrome
- Chronic (>8 weeks) cough:
  - Upper airway cough syndrome
  - Asthma
  - Nonasthmatic eosinophilic bronchitis
  - GERD

In chronic cough, allergies are considered secondary to upper airway cough syndrome or asthma.

When cough has lasted three or more weeks and is not postinfectious, some experts recommend not waiting for eight weeks to begin a chronic cough workup [6].

PATIENT HISTORY

A detailed evaluation is performed and should include the following [2; 5; 6; 8; 10; 100]:

- Presenting symptoms or cough characteristics:
  - Duration
  - Productive or nonproductive
  - Associated symptoms (e.g., rhinorrhea, nasal congestion, sneeze, fever, sputum production, hemoptysis, dyspnea, weight loss, dysphonia, dysphagia, peripheral edema)
  - Prior episodes
  - Preceding illnesses (e.g., recent viral infection)
  - Clarify whether the patient is coughing, throat-clearing, or both.
- Medical history, including pulmonary and extrapulmonary (e.g., GERD, hypertension, allergic, immune) conditions
- Surgical history, especially involving cardiac, pulmonary, gastrointestinal, and otolaryngological organ systems
- Family history of atopic disease
- Exposure history
  - Tobacco and cannabis smoking or vaping (e.g., electronic cigarettes)
  - Occupational and environmental exposures
  - Recent travel
  - Country of origin
  - Potential sick contacts
- Review current medications for potential iatrogenic cause. Ask about current use of both prescribed and over-the-counter NSAIDs and aspirin.

It is important to always rule out culprit medications by assessing whether the patient is taking an ACE inhibitor antihypertensive, NSAID, sitagliptin, or any medication that may be suspected of inducing the cough. A dry persistent cough from ACE inhibitor use is caused by bradykinin, substance P, and prostaglandins that accumulate in the upper respiratory tract or lung when ACE is inhibited, enhancing the cough reflex. Stopping the drug typically resolves coughing within four weeks or improves it sufficiently for a diagnosis of iatrogenic cough. Switching to angiotensin II receptor blockers (ARBs) provides antihypertensive control without provoking coughing [6; 101].

PHYSICAL EXAMINATION

The physical examination of a patient presenting with chronic should assess for nasal congestion, pharyngeal erythema, tonsillar swelling, hoarseness, stridor, wheeze (particularly focal wheeze), crackles, and other adventitious sounds.

MANDATORY INITIAL TESTS

Initial diagnostic testing should include chest radiography (usually x-ray). Spirometry testing of pulmonary function is recommended pre- and post-bronchodilator to evaluate possible asthma or COPD.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Respiratory Society suggests that clinicians do not routinely perform a chest CT scan in patients with chronic cough who have normal chest radiograph and physical examination.

(https://erj.ersjournals.com/content/55/1/1901136. Last accessed August 12, 2024.)

Strength of Recommendation/Level of Evidence: Conditional recommendation, very low-quality evidence

"RED FLAG" ASSESSMENT OF SERIOUS UNDERLYING CAUSES OF COUGH

What findings on the initial evaluation of chronic cough require further evaluation?

In cough of any duration, the initial evaluation should identify any danger signs that may indicate a diagnosis requiring urgent attention. Important danger signs that will need further evaluation with chest x-ray and possibly laboratory testing and computed tomography (CT) include [44; 100]:

- Systemic symptoms (raises suspicion for chronic infection or rheumatic disease):
  - Fever
  - Night sweats
  - Weight loss
  - Peripheral edema with weight gain
- Hemoptysis, an indicator of infection (e.g., bronchiectasis, lung abscess, tuberculosis), cancer (e.g., lung, bronchus, or larynx), rheumatologic diseases, heart failure, or foreign body inhalation
- Prominent dyspnea, especially at rest or at night, a possible clue to airway obstruction or lung parenchymal disease
- Possible foreign-body inhalation (requires urgent bronchoscopy)
- Smoker older than 45 years of age with a new cough, change in cough, or co-occurring voice disturbance
- Hoarseness
- Trouble swallowing when eating or drinking
- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough

EVALUATION OF COMMON CAUSES OF CHRONIC COUGH				
Evaluation	**Common Causes**			
	Asthma	**NAEB**	**UACS**	**GERD**
Spirometry	X			
Bronchodilator reversibility	X			
Bronchoprovocation challenge	X			
Allergy evaluation	X	X	X	
Sputum eosinophilia		X		
Blood eosinophilia		X		
Fractional exhaled nitric oxide (FeNO)		X		
Sinus imaging			X	
Nasopharyngoscopy			X	
Empiric treatment trials[a]	X	X	X	X
[a]Diagnostic-Therapeutic Trials				
UACS	First-generation oral antihistamines Inhaled corticosteroids Inhaled ipratropium			
Asthma or NAEB	Inhaled corticosteroids Systemic (oral) corticosteroids Leukotriene receptor antagonist			
GERD	High-dose proton pump inhibitor (PPI) acid-suppression therapy Anti-reflux lifestyle measures Pro-kinetic agent: metoclopramide			
GERD = gastroesophageal reflux disease; NAEB = nonasthmatic eosinophilic bronchitis; UACS = upper airway cough syndrome.				
Source: [1; 82; 83; 100]				*Table 3*

RECORDS REVIEW

If patients have undergone prior evaluations for upper airway cough syndrome, asthma, GERD, or nonasthmatic eosinophilic bronchitis, obtain and review these medical records, including laboratory values, diagnostic reports, and treatments prescribed, to determine if these etiologies have been accurately assessed, diagnosed, and treated. Patients may not have been completely evaluated for these conditions yet diagnosed based on their response (or lack thereof) to empiric trials, which is important to ascertain [2].

THE ANATOMIC DIAGNOSTIC PROTOCOL (ADP)

Even in current international guidelines that emphasize treatable traits, the anatomic diagnostic protocol (ADP) remains useful in the clinical workup of patients with chronic cough for identifying possible treatable conditions, while recognizing that treatment of the presumed cause(s) does not always improve the cough [19]. Consistent with the ADP, this section organizes chronic cough etiologies and management by their lower airway, upper airway, and gastroesophageal origin.

In nonsmoking, immunocompetent patients not taking an ACE inhibitor and with unremarkable chest radiography, cough lasting longer than eight weeks is considered a symptom of asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, GERD, or any combination [6]. These four common causes to consider should be evaluated (***Table 3***).

The ADP has been modified to simplify the clinical workup by emphasizing empiric treatment trials for suspected, but not fully investigated or confirmed, disease [77]. According to the rationale, objective diagnostic methods for upper airway cough syndrome, asthma, nonasthmatic eosinophilic bronchitis, and GERD are technically demanding, sometimes difficult for patients, and require specialized instruments and personnel. Further, with GERD, discerning causal and temporal relationships between acid reflux and cough is difficult. Thus, sequential empirical therapy is frequently considered and is advised by some before embarking on extensive workup [39; 102]. Because symptom reduction is said to confirm a diagnosis, empiric treatment has been called a diagnostic-therapeutic trial [1].

DIAGNOSTIC TESTS

If airway disease is suspected, the treatable traits approach is advocated to identify and optimize treatment of pulmonary, extrapulmonary, and behavioral traits (***Table 4***). Optimizing airway disease treatment is usually the key to managing cough in these patients. Cough hypersensitivity may be a trait in airway disease and require additional specific treatment [5].

Classic asthma, cough-variant asthma, and nonasthmatic eosinophilic bronchitis are clinical diagnoses with no clear-cut, absolute diagnostic test available to either rule asthma in or out as the cause of a patient's chronic cough [10]. In a stepwise diagnostic approach, initial abnormal lung function testing suggests classic asthma or COPD; normal testing is inclusive of cough-variant asthma, nonasthmatic eosinophilic bronchitis, or chronic bronchitis. Absence of bronchial hyperreactivity to methacholine challenge in patients with normal physical exam and spirometry findings suggests nonasthmatic eosinophilic bronchitis. Negative airway responsiveness can exclude cough-variant asthma. Abnormal spirometry contraindicates bronchial challenge testing [104].

Lung Function Tests

Spirometry can reveal airflow obstruction, variability (>20%) in peak expiratory flow measurements, or an improvement in threshold testing (FEV1 >12%, improvement from baseline of >200 mL) in response to bronchodilators (b-2 agonists). Abnormal spirometry can be seen in patients with classic asthma and COPD, but not cough-variant asthma or nonasthmatic eosinophilic bronchitis [104].

Spirometry

An FEV1/forced vital capacity (FVC) ratio of <70% (or below the lower limit of normal, if available) is a positive test for obstructive airway disease (obstructive spirometry) [103].

Bronchodilator Reversibility Test

Bronchodilator reversibility testing is recommended in patients with obstructive spirometry (FEV1/FVC ratio <70%). Following short-acting beta-agonist bronchodilator administration, improvement in FEV1 of ≥12%, together with an increase in volume of ≥200 mL, is a positive test [103].

Airway Inflammation Measures

Asthma is often, but not always, mediated by eosinophilic inflammation, and measurement of airway inflammation has clinical utility because eosinophilic airway inflammation is associated with favorable inhaled corticosteroid response. Fractional exhaled nitric oxide (FeNO) levels and peripheral blood eosinophil count indirectly estimate airway eosinophilia [5; 10; 84]

Significant (>3%) sputum eosinophilia is the criterion standard for eosinophilic inflammation, but sputum eosinophilia may not be routinely available. Blood eosinophil count is simple and readily available but has diurnal and seasonal variability so multiple assessments should be performed. A blood eosinophil count >0.3 cells/mcL may indicate eosinophilic airway inflammation.

FeNO is a surrogate marker of eosinophilic airway inflammation and inhaled corticosteroid response in classic asthma. FeNO has a relatively high specificity in predicting asthma among patients with chronic cough, but a cut-off level for diagnosis lacks consensus. Elevated FeNO levels (>40 ppb) support a diagnosis of asthma with typical symptoms, but the usefulness in predicting inhaled corticosteroid response in chronic cough is uncertain [5].

A meta-analysis of studies in patients with chronic cough reported significantly higher inhaled corticosteroid response rates in high (>25 ppb) compared with low FeNO (87.4% vs. 46.3%) [105]. After three weeks of high-dose inhaled corticosteroids, the response rate (defined as a ≥1.3-point increase in LCQ) was 68% in patients with high FeNO and no other apparent etiology; LCQ scores and FeNO significantly improved. However, improvements in cough were unrelated to changes in FeNO levels, challenging their direct mechanistic link [106]. Thus, an inhaled corticosteroid trial should be prompted with FeNO >25 ppb but avoided with FeNO <25 ppb unless other factors suggest eosinophilic airway disease [5]. Treatment decisions should not solely hinge on FeNO values [6].

Airway Hyper-Reactivity Measures

In patients with negative physical examination and spirometry findings, bronchial challenge testing (e.g., methacholine) should be performed to confirm airway hyper-reactivity consistent with symptomatic asthma [84]. Bronchial challenge testing is recommended in patients with reactive airway diseases to help diagnosis of asthma and nonasthmatic eosinophilic bronchitis as a cause of chronic cough. A negative bronchial challenge test (defined as an FEV1 decrease of <20% at the highest methacholine challenge dose [10 mg/mL]) has a high negative predictive value of asthma as an etiological diagnosis in chronic cough [104].

Airway eosinophilic inflammation can be present in both asthma and nonasthmatic eosinophilic bronchitis but can be distinguished by a methacholine inhalational challenge (positive in asthma, negative in nonasthmatic eosinophilic bronchitis) because substantially more mast cells localize in the smooth muscle layer in asthma compared with nonasthmatic eosinophilic bronchitis [6].

AIRWAY INVESTIGATIONS IN PATIENTS WITH CHRONIC COUGH		
Investigation	**Description**	**Utility**
Lower Airway		
Chest radiograph	Plain radiograph of the chest from anterior or posterior aspect (occasionally lateral view)	**Mandatory**. Abnormal findings should be pursued first as potential cause of chronic cough.
Spirometry	Maximal inhalation and exhalation into a spirometer measures forced expiratory volume in one second (FEV1) and forced vital capacity (FVC)	**Mandatory** test for airflow obstruction. FEV1 ≤80% or FEV1/FVC ratio <70% predicted for age and sex prompts reversibility testing.
Bronchodilator reversibility test	Pre- and post-bronchodilator spirometry in patients with obstructive airflow to measure change 10 to 15 minutes after SABA (e.g., albuterol)	Increase in FEV1 ≥12%, or ≥200 mL, after SABA indicates reversibility. Ideally, perform before starting asthma therapy.
Fractional exhaled nitric oxide (FeNO)	Measurement of nitric oxide levels in exhaled breath to indicate eosinophilic airway inflammation	Increased FeNO levels correlate with type 2 airway inflammation in asthma or nonasthmatic eosinophilic bronchitis. High FeNO (>30 ppb) may predict corticosteroids response.
Induced airway sputum	Patient inhales nebulized hypertonic saline (3% to 5%), inducing sputum expectoration for differential cell count analysis.	The criterion standard assessment of eosinophilic airway, routinely used in cough clinics but not widely adopted
Bronchial challenge/ provocation test	Patient inhales histamine or methacholine; a ≥20% drop in FEV1 confirms bronchial hyperresponsiveness (positive test).	Positive test with isolated cough and normal spirometry indicates an anti-asthma therapy trial. A negative test makes asthma improbable.
Chest computed tomography (CT)	Provides better resolution of lung parenchymal and mediastinal structures than chest x-ray	In productive cough, may identify early lung fibrosis or confirm bronchiectasis. Low utility in chronic cough with normal physical exam and chest x-ray.
Bronchoscopy (fiberoptic)	Allows direct visualization of the upper and lower airways and bronchoalveolar lavage to obtain specimens	**Mandatory** in all patients with suspected inhaled foreign body. Endobronchial appearance typically normal in chronic cough with normal chest x-ray.
Upper Airway		
Laryngoscopy (fiberoptic)	Allows direct inspection of laryngopharyngeal area including epiglottis and vocal cords	Typically unremarkable, but may reveal laryngopharyngeal reflux. Suspected laryngeal dysfunction prompts challenge laryngoscopy.
Sinus CT imaging	Visualizes the frontal, ethmoid, and maxillary sinuses and nasal passages	May provide evidence of sinus opacification or mucosal thickening. Unclear role in patients with chronic cough without nasal symptoms.
Other		
Peripheral blood eosinophil count	Measures absolute number or relative percentage of eosinophils in peripheral blood	May help predict corticosteroid response in respiratory diseases; utility in chronic cough not established.
ppb = parts per billion, SABA = short-acting beta-agonist.		
Source: [10; 19; 103]		*Table 4*

IDENTIFICATION AND MANAGEMENT OF UNDERLYING ETIOLOGIES

The concept that chronic cough is a disease in its own right has only recently gained acceptance. Different phenotypes of this condition are recognized (e.g., asthmatic cough, reflux cough), but the underlying pathology involves hypersensitivity of the vagus nerve and its central projections. The paradigm of asthma, GERD, and postnasal drip causing the symptom of chronic cough was promulgated from the 1980s onwards. However, after it became apparent that many patients suffering from chronic cough with a particular disease label (e.g., asthma, GERD) failed to respond to treatments for that condition, clinical practice guidance changed [79].

Systematic evaluation and treatment guidelines for chronic cough, based on the anatomic locations of receptors and afferent pathways in the cough reflex, first appeared in 1977 [80]. Using such an approach was estimated to determine the cause of chronic cough in 100% of patients, and the subsequent cause-specific treatment was reportedly almost always successful. Termed the ADP, this stepwise diagnostic approach involves a targeted patient history and physical examination to investigate the possible cause/s of their cough. This information is then used to initiate a stepwise treatment approach until resolution of the cough symptoms [77].

The ACCP recommended the ADP in their comprehensive clinical practice guideline on cough in 1998 and in 2006 [81; 82]. More recent ACCP guidelines evaluate ADP components and provide treatment recommendations on the major causes of cough, including chronic cough due to GERD in 2016, asthma and nonasthmatic eosinophilic bronchitis in 2020, stable chronic bronchitis in 2020, and unexplained/refractory chronic cough in 2016 [77; 83; 84; 85; 86].

However, the understanding of chronic cough has evolved beyond the ADP, especially since 2020 with incorporation of cough hypersensitivity and the treatable traits approach into clinical practice guidelines and endotyping of many cough-associated chronic inflammatory conditions. These knowledge advances are not efficiently reaching U.S. clinicians, because ACCP guidelines on chronic cough have not kept pace. While the ADP remains an important structure of the diagnostic workup for chronic cough patients, its assumptions have been supplanted in recent international chronic cough guidelines.

THE "TREATABLE TRAITS" APPROACH IN CHRONIC AIRWAY DISEASES

In the context of the treatable traits approach, how is a trait defined?

In the late 19th century, Sir William Osler established the modern approach to the diagnosis and treatment of disease, based on the principal organ system where symptoms and signs manifest, with some biological correlates. The Oslerian paradigm of disease classification using diagnostic categories has been in use for more than 100 years, with substantial merit, but limitations of the diagnostic label approach have become evident [16].

As noted, in 2016, the treatable traits approach was introduced to pulmonary medicine to overcome the shortcomings of the diagnostic label approach, which does not consider the biological complexity of airway diseases, the distinct endotypes present in each patient, or common patterns of disease such as chronic cough [14; 17].

The treatable traits approach addresses the complexity of chronic airway diseases as heterogeneous, frequently overlapping, and often comorbid conditions. In clinical trials of patients with asthma and COPD, the treatable traits approach led to significantly greater improvements in health-related quality of life and biological outcomes and reductions in primary care visits (compared with usual care) [16].

A trait is defined as clinically relevant, measurable, and treatable. These traits can be identified by their phenotypes and/or endotypes in pulmonary, extrapulmonary, and behavioral/environmental domains, and can coexist, interact, and change over time in the same patient. The treatable traits approach is agnostic to the traditional diagnostic labels of asthma or COPD and can be used in any patient with airway disease. The treatable traits approach often extends beyond the diagnostic label itself to find more treatment targets, especially in complex patients with suboptimal response to conventional guideline-based treatment [87; 88]. In other words, the treatable traits approach represents a transdiagnostic model.

In asthma, many extrapulmonary traits present as connected comorbidities, meaning they coexist with asthma and may share mechanisms. Extrapulmonary traits (e.g., chronic rhinosinusitis, GERD, anxiety, atopic dermatitis) are clinically relevant as they predict poor outcomes, confound the management of asthma, and are treatable themselves. Through multidimensional assessment of pulmonary, extrapulmonary, and behavioral/environmental domains, the treatable traits approach identifies and targets extrapulmonary traits with effective treatments, improving both asthma and the comorbidity [89].

In the 1970s, the ADP extended the Oslerian classification system to cough, addressing the three common causes (asthma, postnasal drip, reflux) arising from three different anatomical areas. Refined to four causes (asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and GERD), this approach benefitted many patients, but in 30% to 40% of these patients, the coughing continues or a presumed cause cannot be identified [16; 90]. In 2023, COPD was added to become a fifth common potential underlying cause of chronic cough [24].

Chronic cough is associated with airway and reflux diseases that are heterogeneous, frequently overlapping, and often comorbid, the same characteristics the treatable traits approach addresses [14; 17]. For instance, asthma is a clinical syndrome with varying phenotypes and endotypes, rather than a single disease entity. COPD is an umbrella term encompassing different respiratory conditions sharing airflow obstruction. Asthma is not always eosinophilic, and GERD is not necessarily acidic [15]. Despite its relatively recent appearance, the treatable traits paradigm is endorsed throughout pulmonary medicine and in post-2019 (international) clinical practice guidelines on chronic cough.

ENDOTYPES OF COUGH-RELATED CHRONIC INFLAMMATORY DISEASES

A phenotype is an observed characteristic resulting from interactions between genotype and environment. An endotype is a specific biological pathway that forms the basis of observable traits in the phenotype [56].

In the 2016 treatable traits paper, the authors broadly call for a shift away from the classical Oslerian top-to-bottom approach (i.e., from symptoms to mechanisms) to reclassifying airway diseases bottom-up, by linking causal molecular pathways (i.e., endotypes) to disease phenotypes (i.e., from molecules to symptoms) [14].

This has been unfolding in allergy and immunology, and these advances are highly relevant to pulmonary medicine and to chronic cough. For instance, the chronic inflammatory diseases of asthma, allergic rhinitis, chronic rhinosinusitis with or without nasal polyposis, eosinophilic esophagitis, and atopic dermatitis, are now defined by a constellation of symptoms that may result from different pathological mechanisms and not as homogeneous diseases [91].

The discovery of new endotypes in allergic and immune diseases has prompted the transition from symptom-focused disease descriptions to biomarkers and pathogenetic pathways—from phenotypes to endotypes [91]. The imperative for transitioning to endotypes is heightened by FDA approval of several biologicals that target specific inflammatory pathways important in disease pathophysiology [92]. These include the most common chronic cough-associated disorders.

Immune dysregulation has been endotyped as type 1, type 2, and type 3 responses. Asthma has been commonly dichotomized as type 2 and non-type 2. Type 2 inflammation is the best-characterized endotype [91; 93; 94; 95].

Type 2 inflammation involves eosinophils as the key players, which contribute to chronic allergic inflammation by producing cytokines, or interleukins (IL), with specific roles in the inflammatory pathway. IL-5 promotes eosinophil recruitment to sites of inflammation. IL-4 and IL-13 promote immunoglobulin E (IgE) production and immune cell trafficking to tissue, driving and sustaining the type 2 response, tissue damage, and chronic inflammation. IL-31 activates binding sites on sensory neurons, which release CGRP and nerve growth factor, causing neurogenic inflammation. In non-type 2 asthma, Th2 cells migrate to asthmatic bronchi and change their phenotype to produce T1 effector cytokines, such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), inducing bronchial epithelial apoptosis and remodeling. TNF-α promotes neutrophilic inflammation, which correlates with sputum TNF-α levels in patients with severe asthma. In type 3 inflammation, innate lymphoid cells type 3 (ILC3), T helper lymphocyte type 17 (Th17), and Th22 cells produce cytokines IL-17, IL-22, and IL-23. This mechanism is particularly relevant in the pathogenesis of chronic rhinosinusitis with nasal polyps and neutrophilic asthma [91; 93; 94; 95].

In 2023, the European Academy of Allergy and Clinical Immunology (EAACI) published an updated disease taxonomy with advances in biomarkers, pathogenetic and metabolic pathways, and pathogenic genetic variants. This expanded nomenclature characterizes the following types with relevance to chronic cough [91].

Type V: Epithelial Barrier Defect

The epithelial barrier defect and microbial dysbiosis lead to dysregulation of the immune response, including extensive activation and release of inflammatory cytokines, chemokines and inflammatory mediators (histamine, leukotrienes, reactive oxygen species). The sequence of events eventually leads to tissue damage in asthma, chronic allergic rhinitis, chronic rhinosinusitis, and chronic rhinosinusitis with nasal polyps.

Type VI: Metabolic-Induced Immune Dysregulation

Obesity is a distinguishing variable for clustering and classifying asthma subtypes, and the number of obese patients with asthma has risen dramatically with increasing obesity rates. The obese asthmatic, more likely to be female with adult-onset asthma and to become corticosteroid resistant, has a higher risk of being hospitalized and more frequently presents with severe disease. Higher body mass index (BMI) is associated with increased circulating inflammatory mediators, blood neutrophils, and eosinophils. An additive effect of asthma and obesity further increases inflammatory mediators and airway inflammation.

An asthma endotype introduced in 2020, IL-6-high asthma, is characterized by elevated plasma IL-6 levels, increased markers of systemic inflammation, metabolic dysfunction, and obesity [96].

Type VII: Inflammatory Drug Reactions

These idiosyncratic reactions include hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and phenotypes such as NSAIDs-exacerbated respiratory disease in patients with asthma and/or chronic rhinosinusitis ± nasal polyposis. NSAIDs-exacerbated respiratory disease is a chronic inflammatory condition characterized by the triad of asthma, recurrent nasal polyps and hypersensitivity to NSAIDs/aspirin. In the underlying mechanism, cyclooxygenase (COX)-1 inhibition releases eicosanoid mediators, causing bronchoconstriction, increased vascular permeability, mucus production and recruitment of inflammatory cells.

These advances in endotyping chronic inflammatory diseases associated with chronic cough have not yet appeared in practice guidelines on chronic cough, with the exception of eosinophilic airway inflammation, but this science is being translated into practice. For example, cough is the most troublesome symptom for patients with asthma. Older patients with asthma and chronic cough show worse clinical outcomes in asthma control, quality of life, and airway obstruction, and more frequent moderate-to-severe exacerbations, partly explained by the interaction of chronic coughing with aging [97]. Non-type 2 inflammation (e.g., increased neutrophils) is associated with cough in older patients with asthma with chronic cough. Interferon-γ is a non-type 2 biomarker that enhances cough reflex sensitivity by inducing calcium influx in vagal sensory neurons and is associated with increased cough in patients with refractory chronic cough. Older patients with asthma show increased levels of sputum IFN-γ. Non-type 2 inflammation (i.e., neutrophils and IFN-γ) is also associated with reduced inhaled corticosteroid response [54; 97; 98].

TREATMENT

CHRONIC AIRWAY INFLAMMATION

Treatment of chronic airway inflammation includes inhaled corticosteroids, long-acting beta-agonists, long-acting muscarinic antagonists, leukotriene receptor antagonists, systemic corticosteroids, and biologicals. Confirmation that chronic cough is due to asthma (or another chronic cough-associated condition) requires a beneficial response to therapy for asthma, as patients with asthma can also have chronic cough due to non-asthmatic causes [44].

For chronic cough due to cough-variant asthma or nonasthmatic eosinophilic bronchitis, the ACCP recommends inhaled corticosteroids as first-line treatment [84]. With incomplete response, the inhaled corticosteroid dose should be escalated and adding a leukotriene receptor antagonist should be considered. Other causes of cough should be reconsidered as well. For cough-variant asthma, adding beta-agonists should be considered.

In patients with chronic cough in asthma, the first-line treatment is inhaled corticosteroid with or without long-acting beta-agonist [6]. A leukotriene receptor antagonist or long-acting muscarinic antagonist may be added in for those who do not fully respond to initial treatment. Whether biologics can treat chronic cough related to asthma has not been studied.

In adult and adolescent patients with chronic cough due to non-asthmatic eosinophilic bronchitis (NAEB), we suggest inhaled corticosteroids as first-choice treatment

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Strength of Recommendation/Level of Evidence: 2B (Weak recommendation based on moderate-quality evidence)

When an offending allergen cannot be identified or avoided, chronic cough associated with nonasthmatic eosinophilic bronchitis should be treated with an inhaled corticosteroid. Second-line therapy calls for escalation of the inhaled corticosteroid dose; if response remains incomplete, the patient should be assessed for other causes of cough and a trial of leukotriene receptor antagonist initiated. Occasionally, systemic corticosteroids may be needed.

Tiotropium may be another therapeutic option. In 17 patients with chronic asthmatic cough refractory to inhaled corticosteroid/long-acting beta-agonist, four to eight weeks of tiotropium (5 mcg/day) significantly improved cough reflex sensitivity and cough severity in a subgroup of 11 patients [107]. These results were replicated in a randomized comparison to theophylline 400 mg/day over four weeks. Both drugs improved cough severity and cough-specific quality of life. Tiotropium decreased cough reflex sensitivity, which correlated with changes in cough severity, and higher baseline cough reflex sensitivity predicted greater tiotropium response. The authors conclude that tiotropium may modulate cough reflex sensitivity to alleviate chronic cough in asthma refractory to inhaled corticosteroid/long-acting beta-agonist [108].

EMPIRIC TREATMENT APPROACH

Empiric treatment of chronic cough is systematically directed at the four most common causes of cough, starting with upper airway cough syndrome. In its 2006 guideline, the ACCP states that therapy should be given in sequential and additive steps, because more than one cause of cough may be present [82]. Initial empiric treatment should begin with an oral first-generation antihistamine/decongestant.

If chronic cough persists after treatment for upper airway cough syndrome, asthma as the possible cause should be worked up next. If spirometry does not indicate reversible airflow obstruction, bronchoprovocation testing is performed in the evaluation for asthma.

With the diagnoses of upper airway cough syndrome and asthma ruled out or treated without the elimination of cough, nonasthmatic eosinophilic bronchitis should be considered next, with a properly performed induced sputum test for eosinophils. In most patients with suspected cough due to asthma, a bronchoprovocation challenge should be performed and, if the result is positive, some combination of inhaled corticosteroids, inhaled beta-agonists, and/or oral leukotriene inhibitors should be administered.

In patients whose cough responds only partially or not at all to interventions for upper airway cough syndrome and asthma or nonasthmatic eosinophilic bronchitis, treatment for GERD should be instituted next. In patients with cough whose condition remains undiagnosed after all of these conditions has been worked up, referral to a cough specialist is indicated.

When the cause of chronic cough is identified or suspected, there are two options [26; 44; 57; 109]. The first is to pursue one diagnostic and treatment path at a time; with incomplete response of the cough to one line of therapy, adding therapy for the next most likely diagnosis is reasonable. The second option in patients with more than one suspected cause and a cough that is especially disruptive is to empirically treat or evaluate the likely causes simultaneously. After the cough resolves, treatments can be stopped sequentially, starting with the least likely to have been helpful, observing the patient for any return of cough.

BEHAVIORAL TREATABLE TRAITS

Nonadherence and poor inhalation technique strongly influence outcomes in airway disease. Despite their critical importance, the proportion of patients with poor technique is high, unimproved over the past 40 years, and often unaddressed by clinicians. These behavioral treatable traits can be improved using strategies such as patient-centered communication, motivational interviewing, shared decision-making, and simplification of drug regimens; and should be assessed in every follow-up visit [110].

Smoking cessation improves cough by resolving chronic bronchitis. Nicotine suppresses the cough reflex, and nicotine withdrawal due to smoking cessation may enhancement cough hypersensitivity; hence, patients may experience more coughing for a period after quitting. This can be attenuated and quit rates improved by using nicotine replacement [5].

LOWER AIRWAY ETIOLOGIES OF CHRONIC COUGH AND MANAGEMENT

Lower airway diseases commonly associated with chronic cough are classic asthma, cough-variant asthma, nonasthmatic eosinophilic bronchitis, and COPD [20].

Chronic cough is a central feature that develops in diverse pulmonary pathologies, such as asthma (an inflammatory airway disease) and idiopathic pulmonary fibrosis (an alveolar fibrosing disease), highlighting the significant role of dysregulated cough pathways in lung disease phenotypes [60]. Chronic cough prevalences have been reported for asthma (8% to 58%), COPD (10% to 74%), bronchiectasis (82% to 98%), interstitial lung disease (50% to 89%) and sarcoidosis (3% to 64%); in all five diseases, patients demonstrate cough reflex hypersensitivity, a cardinal feature of cough hypersensitivity syndrome [111].

Presence of chronic cough generally predicts impaired health status and more severe respiratory disease and is associated with greater symptom burden and disease severity in asthma, COPD, bronchiectasis, and interstitial lung disease. It has also been linked to greater exacerbations in asthma and bronchiectasis and increased mortality and lung transplantation in idiopathic pulmonary fibrosis [111].

Asthma and Nonasthmatic Eosinophilic Bronchitis

Asthma is a complex, chronic airway inflammatory disease of bronchial hyper-responsiveness, intermittent airflow obstruction, and symptoms of wheeze and dyspnea that impacts 26 million people in the United States, results in approximately 10,000 deaths annually, incurs an estimated $56 billion annually in medical care and lost productivity costs, and accounts for cough in 24% to 32% of adult nonsmokers with chronic cough [84; 112; 113]. Asthma prevalence has increased with rising obesity rates. Obesity often precedes an asthma diagnosis, making it an important modifiable risk factor (or treatable trait) [5; 113].

In atopic asthma, the most common type (affecting approximately 50% of adults with asthma), allergens trigger innate and adaptive immune activity, releasing inflammatory mediators such as histamine, prostaglandins, and leukotrienes that promote bronchoconstriction and cough [20; 114]. Classic asthma describes symptoms of wheezing, chest tightness, and dyspnea. In these patients, immune response to allergen exposure results in airway inflammation, airflow obstruction, and characteristic symptoms. Increased mucous secretions in narrowing airways induce cough [31; 112].

Cough-variant asthma, in contrast, presents with persistent cough as the primary or only symptom. Cough receptor density is highest in the proximal airways, decreasing as the airways get smaller. In cough-variant asthma, inflammation is primarily in the proximal airways, where cough is stimulated, and less so distally, where inflammation and narrowing cause wheezing and dyspnea in classic asthma [31; 56]. Some have

suggested that asthma-variant cough is a more appropriate term than cough-variant asthma, given that cough hypersensitivity symptoms are the chief complaints, while asthmatic features act as triggers and treatable traits of chronic cough in these patients [115].

Nonasthmatic eosinophilic bronchitis was first described in 1989 as corticosteroid-responsive chronic cough in nonsmokers with airway eosinophilia, but without variable airway obstruction or bronchial hyper-responsiveness [116]. Nonasthmatic eosinophilic bronchitis accounts for 10% to 30% of specialist referrals for chronic cough, but nonasthmatic eosinophilic bronchitis prevalence is uncertain, as its diagnosis requires assessment of eosinophilic airway inflammation [44; 84; 117]. In nonasthmatic eosinophilic bronchitis, patients have chronic cough, no symptoms or evidence of variable airflow obstruction, sputum eosinophilia, and normal bronchial provocation tests [56; 117].

Chronic cough in asthma is mechanistically complex, involving IgE or non-IgE mediated eosinophilic airway (i.e., atopic or nonatopic) inflammation, abnormal neuromechanical properties of the lungs, and presence of cough reflex hypersensitivity independently of airway eosinophilia or bronchial hyper-responsiveness [20].

Nonasthmatic eosinophilic bronchitis and asthma share airway eosinophilia and similar basal membrane thickening, but inflammatory mast cells primarily infiltrate the superficial airway epithelium in nonasthmatic eosinophilic bronchitis versus airway smooth muscle in asthma. Along with lower IL-13 expression in nonasthmatic eosinophilic bronchitis, this partially explains bronchitis and cough with normal airway responsiveness in nonasthmatic eosinophilic bronchitis [116; 118]. Nonasthmatic eosinophilic bronchitis lacks the airway hyper-responsiveness of cough-variant asthma, but both share atopic features of eosinophilia and airway inflammation [109].

Eosinophilic airway inflammation in cough-variant asthma is linked to more severe disease. Cough-variant asthma may be a precursor of classic asthma, and both cough phenotypes can manifest overlapping symptoms, airway inflammation, and bronchial hyper-responsiveness [20]. Chronic dry cough, eosinophilic inflammation, and chronic airflow obstruction can present in both cough-variant asthma and nonasthmatic eosinophilic bronchitis [56].

Chronic Obstructive Pulmonary Disease (COPD)

COPD comprises several lung diseases, including emphysema and chronic bronchitis, with persistent and usually progressive airflow limitation associated with an enhanced chronic inflammatory response in the airways and lungs. Exacerbations and comorbidities contribute to the overall severity, while airway and systemic inflammation in COPD is related to disease progression and mortality [119; 120].

In the United States, 14.2 million adults had diagnosed COPD in 2021, of whom 25% were never-smokers, and COPD accounted for 354,000 deaths in 2020 [121; 122]. Among patients with COPD, 70% experience persistent cough and many consider it extremely severe and impairing [64].

Chronic bronchitis describes productive cough on most days of the week for at least three months total duration in two successive years. Chronic obstructive bronchitis is chronic bronchitis with spirometric evidence of airflow obstruction. Chronic asthmatic bronchitis is a similar condition with chronic productive cough, wheezing, and partially reversible airflow obstruction mostly found in smokers with a history of asthma [123].

Emphysema is defined as the permanent enlargement and damage of the lung air sacs with destruction of the airspace walls, causing symptoms of breathlessness. Emphysema can exist without airflow obstruction but is more common in patients with moderate or severe airflow obstruction [119].

COPD manifests as productive cough with airflow limitation and occasional bronchial hyper-responsiveness [20]. COPD and asthma share symptoms of cough, wheeze, and difficulty breathing. The blurred distinction between chronic obstructive bronchitis and chronic asthmatic bronchitis is termed asthma-COPD overlap [123].

Cigarette smoking is the primary risk factor, but only 15% of smokers develop clinically apparent COPD. Smokers with pre-existing airway reactivity, even in the absence of clinical asthma, have greater risk of developing COPD. Inflammation in the large and small airways can persist after smoking cessation. The genetic disorder alpha-1 antitrypsin deficiency is an important cause of emphysema in nonsmokers and markedly increases susceptibility to COPD in smokers [120; 123].

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is an interstitial lung disease, a group of pulmonary disorders characterized by inflammation and/or fibrosis of the lung parenchyma associated with progressive dyspnea frequently resulting in end-stage respiratory failure. Interstitial lung disease affects 650,000 people and causes 25,000 to 30,000 deaths per year in the United States [124].

Idiopathic pulmonary fibrosis, the most common interstitial lung disease accounting for 35% to 61% of all patients, is a chronic, progressive, invariably fatal fibrotic lung disease [111; 124]. Despite approvals of two antifibrotic therapies, the five-year survival rate remains 25%, far worse than many common cancers. Pharmacotherapies slow the disease progression, but none address the significant symptoms of chronic cough, fatigue, and dyspnea suffered by 85% to 95% of patients with idiopathic pulmonary fibrosis [125].

DISTINGUISHING CHARACTERISTICS OF RHINITIS PHENOTYPES				
Rhinitis Phenotype	**Primary Symptoms**	**Associated Features**	**More Responsive to**	**Less Responsive to**
Allergic	Sneezing, nasal pruritis, clear rhinitis	Ocular itching, wheezing, atopic dermatitis	INCS, INAH, FGAH, SGAH, SCS, AIT	Decongestants, ABX
Nonallergic noninfectious	Intermittent congestion, clear rhinitis	Physical triggers (temperature changes, food, irritants)	INCA, INAH, INAC	FGAH, SGAH, SCS, AIT, ABX
GERD-associated	Postnasal drip, throat clearing	Epigastric pain, heartburn, dysphagia	GERD diet and lifestyle changes, INAC	FGAH, SGAH, INCS, INAH, SCS, ABX, AIT
Chronic rhinosinusitis with or without nasal polyposis	Anosmia/hyposmia, unremitting congestion, facial pain/pressure	Wheezing, NSAID hypersensitivity	SCS, biologics, intermittent INCS	FGAH, SGAH, INAH
Infectious	Acute onset, sinus pressure, nasal congestion with purulent discharge	Viral prodrome, episodic nature lasting <2 weeks	Saline nasal lavage, INAH, decongestants, INAC	FGAH, SGAH, INCS, SCS, ABX, AIT
ABX = antibiotics; AIT = allergen immunotherapy; FGAH = first-generation oral antihistamines; GERD = gastroesophageal reflux disease; INAC = intranasal anticholinergics; INAH = intranasal antihistamines; INCS = intranasal corticosteroids, SCS = systemic corticosteroids; SGAH = second-generation oral antihistamines.				
Source: [6]				*Table 5*

Chronic cough in idiopathic pulmonary fibrosis predicts disease progression and mortality, is as distressing as breathlessness for patients, and remains one of the most difficult symptoms to control [64; 125]. Among 1,447 patients with idiopathic pulmonary fibrosis cough, every 1-point decrease in LCQ score increased the risk of respiratory-related hospitalization by 6.5%, death by 7.4%, and lung transplantation by 8.7% over 12 months. Worse cough-specific quality of life independently associated with increased risk of respiratory hospitalization, death, and lung transplantation [126].

Two breakthrough studies demonstrated that low-dose morphine and nalbuphine can safely decrease coughing in idiopathic pulmonary fibrosis patients, as will be described later in this course.

Bronchiectasis

Bronchiectasis is a heterogenous disorder characterized by infection, airway inflammation, failure of mucociliary clearance, and airway structural damage. Absolute suppression of cough is not recommended because bronchiectasis is a suppurative condition with an increased risk of infection. However, much of the cough exceeds what is physiologically needed for sputum clearance and is thus maladaptive or pathological [111].

Cough is a central clinical feature of bronchiectasis that contributes to impaired health status and may be an early indicator of disease exacerbation, but it is almost never evaluated [64].

UPPER AIRWAY ETIOLOGIES OF CHRONIC COUGH AND THEIR MANAGEMENT

In upper airway cough syndrome, diverse chronic infectious, inflammatory, or neurogenic upper airway diseases induce chronic cough [20; 127]. While upper airway cough syndrome lacks a uniform definition, its prevalence in chronic cough patients is probably comparable to other major causes like asthma and GERD; in some studies, it is the first or second leading cause [39; 127].

Rhinitis, comprising most chronic upper airway diseases in upper airway cough syndrome, has a lifetime prevalence up to 33% in the United States [6]. Nasal mucosa inflammation due to allergic or non-allergic cause leads to mucus secretion, sneezing, nasal pruritus, and postnasal drip that irritates the airways and stimulates coughing [31]. In chronic rhinitis, these symptoms persist at least three months, inducing nasal obstruction and increased nasal discharge [119].

Rhinitis has numerous phenotypes and the nomenclature is not straightforward (***Table 5***). Allergic rhinitis requires immunoglobulin E (IgE)-mediated sensitization to an allergen exposure [6]. Chronic cough in patients with allergic rhinitis is often related to undiagnosed asthma or nonspecific bronchial hyperreactivity. Bronchial biopsy studies of patients with allergic rhinitis without asthma have shown inflammatory cell infiltration and active structural remodeling of the lower airways similar to that of patients with asthma, thereby potentially contributing to cough in these patients [128].

Chronic nonallergic rhinitis syndromes include chronic nonallergic rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES), atrophic rhinitis, and drug-induced rhinitis; nonallergic rhinitis accounts for up to 80% of cases [129]. Nonallergic rhinitis phenotypes include [6]:

- Vasomotor
- Irritant
- Infectious
- GERD-associated
- Chronic rhinosinusitis with or without nasal polyposis

Rhinosinusitis is preferred to sinusitis because purulent sinus disease without similar rhinitis is rare [130].

Chronic rhinosinusitis is an inflammatory disease of the sinonasal mucosal lining secondary to infectious and allergic etiology, with symptoms of anosmia, nasal obstruction, thick nasal drainage, and facial pressure [92]. Retention of sinus secretions, the key event in chronic rhinosinusitis development, fosters infection and is caused by obstruction or narrowing of sinus ostia, mucociliary dysfunction, or altered mucus composition; 90% of sinus infections involve the maxillary sinus [119]. Cough, one of the important symptoms of chronic rhinosinusitis, occurs in 1% to 5% of U.S. adults [131].

Chronic rhinosinusitis with nasal polyposis, representing up to 20% of chronic rhinosinusitis cases, is more debilitating than the phenotype without nasal polyposis. Comorbidities in chronic rhinosinusitis with nasal polyps are asthma (55% to 56%), allergy (12% to 77%), and allergic rhinitis (17% to 76%). Asthma with nasal polyps is harder to control and more prone to severe exacerbations [92; 93].

Chronic cough pathogenesis in upper airway cough syndrome was previously tied to postnasal drip, because the nose and sinuses lack vagal sensory innervation. However, only a minority of patients with postnasal drip have chronic cough, some patients with upper airway cough syndrome do not have postnasal drip, and the pathophysiology is more complex [11; 127].

In chronic rhinitis and rhinosinusitis, inflammatory mediators are transmitted via glossopharyngeal and vagal receptors in the pharynx and larynx, and via afferent fibers of the trigeminal nerve, sensitizing the cough reflex centrally [11]. Direct irritation of nasolaryngeal mucosa and stimulation of vagal afferents by postnasal drip lead to hematogenous spread of inflammatory mediators and neurogenic or systemic communication between upper and lower airways, resulting in airway sensory nerve inflammation, cough reflex hypersensitivity, and chronic cough [10; 39].

Convergence of trigeminal and vagal afferents in central cough pathways provides a mechanistic/neuronal link between upper airway disease and the development of cough hypersensitivity [5]. In general, upper airway diseases lead to chronic cough only if the cough reflex becomes hypersensitive; therefore, they are generally considered a trigger rather than a cause of chronic cough [11].

In 2024, nonallergic rhinopathy was introduced to replace vasomotor rhinitis as the term describing 80% of the larger nonallergic rhinitis category, prompted by evidence that neuroinflammation and TRPV1 receptor activation play important roles, rather than blood vessels. TRPV1 also contributes to nasal hyper-reactivity in allergic rhinitis, an entity called mixed rhinitis. The management of nonallergic rhinitis requires the correct diagnosis; rhinopathy draws attention to the underlying neuro-immune endotype [129; 132].

Chronic cough is triggered in many patients with chronic upper airway disease (usually allergic rhinitis or chronic rhinosinusitis with or without nasal polyps) with common symptoms and signs of postnasal drip, compulsive throat-clearing, nasal stuffiness, globus feeling, headache/facial pain, loss of smell and taste, recurrent hoarseness, and cobblestone appearance of the pharyngeal mucosa on inspection [11]. The most commonly used tool is the SinoNasal Outcome Test (SNOT) [92].

With numerous symptoms and unclear diagnostic criteria, upper airway cough syndrome diagnosis has been based on first-generation oral antihistamine response, which may have central antitussive effects. Upper airway and other airway disease is frequent in patients with chronic cough, making it unclear whether coughing arises from upper or lower airways [5].

A large case series found allergic rhinitis, classic asthma, chronic rhinosinusitis, and nasal polyposis in 46%, 31%, 12%, and 9% of patients with chronic cough, respectively. The high predictive value for concomitant asthma in upper airway cough syndrome calls for investigating lower airway pathology in chronic cough of upper airway origin [20].

Rhinitis is a principal contributor to upper airway cough syndrome. The lengthy differential diagnosis of rhinitis in upper airway cough syndrome includes both allergic and nonallergic diseases; many patients have a combination of both or mixed rhinitis. Distinguishing these will increase treatment success and decrease the time before symptoms improve [6].

Radiological investigations may be useful and are guided by nasal symptoms. Incidental sinus changes may be present in up to 33% of CT and 67% of MRI scans. PPIs should not be used to treat upper airway symptoms [5].

Laryngeal dysfunction and hypersensitivity are common in chronic cough [5]. Consider treatment of laryngeal hypersensitivity as a symptom of cough hypersensitivity. Laryngitis often leads to chronic cough with voice changes (e.g., hoarseness, aphonia). Chronic cough is frequent in functional voice disorders, (e.g., muscle tension dysphonia) [11].

In vocal cord dysfunction, laryngeal hypersensitivity leads to persistent laryngospasm due to different triggering factors, manifesting as cough, wheeze, breathlessness, and voice disturbance. Coughing can be both a trigger and a symptom. Symptoms may be episodic. Diagnosis is based on findings in history, laryngoscopy, and, if possible, spirometry during an attack [5; 11]. In a refractory chronic cough population, vocal cord dysfunction is a common finding and may be a manifestation of laryngeal hypersensitivity. Treatment is by speech and language therapy intervention [5].

REFLUX DISORDER ETIOLOGIES OF CHRONIC COUGH AND THEIR MANAGEMENT

In GERD, retrograde transit of gastric contents into the esophagus leads to troublesome symptoms of heartburn, esophageal chest pain, and regurgitation (i.e., "typical" esophageal symptoms) [133; 134]. Cough is an extraesophageal symptom of reflux disease [11]. Chronic cough has a low, but potential, pathophysiological relationship to reflux disease [133]. Estimated chronic cough due to GERD vary widely (7% to 85%), with higher prevalence in Western than Asian countries [20]. Chronic cough and GERD are both very common conditions and can therefore co-appear without being causally related [99].

GERD was previously considered a leading chronic cough etiology directly caused by the acidity of proximal esophageal refluxate, but patients with chronic cough and healthy controls show similar proximal reflux events [58; 135]. Many patients with chronic cough report GERD symptoms, but PPI therapy is ineffective in those without acidic reflux and only modestly benefit those with typical esophageal symptoms [109].

Reflux can be acidic or non-acidic, liquid or gaseous, and proximal or distal in location. Reflux can trigger cough, coughing can induce reflux, and chronic cough may also cause GERD or increase reflux episodes [20; 134]. PPIs decrease reflux acidity but not reflux events and work poorly in patients with airway or extraesophageal reflux [136]. PPI failure in chronic cough treatment suggests the acidic component of reflux has little effect on chronic cough or its etiology [58].

In extraesophageal reflux, troublesome symptoms not normally considered esophageal manifest in the lower and upper airways as chronic cough, asthma, laryngitis, dysphonia, pulmonary fibrosis, sinus disease, ear disease, postnasal drip, throat clearing, non-cardiac chest pain, or dental erosion [20; 134].

Laryngopharyngeal reflux is defined as the backflow of weakly or non-acidic "mist" or liquid above the upper esophageal sphincter into the upper airways. Due to weaker mucosal defenses in the upper respiratory tract, inflammation of the mucous membranes and epithelial tissue damage occur with exposure to fewer, and less acidic, reflux events. A significant negative effect from pepsin, a gastric enzyme, on oropharyngeal and respiratory tract tissues is also demonstrated [58; 137].

Airway reflux is interchangeably used for laryngopharyngeal, non-acid esophageal, extraesophageal, and silent reflux. But it is important to remember that airway reflux is not GERD. Defined by the symptoms of heartburn and dyspepsia, and associated with esophagitis, GERD is a peptic condition predominantly of liquid acidic reflux [59]. The majority of patients with airway reflux/laryngopharyngeal reflux do not have esophagitis or heartburn [137].

Airway reflux shifts the paradigm from traditional GERD to cough hypersensitivity through sensitization of vagal afferents. Evidence that esophageal irritation by acid and non-acid reflux may directly initiate cough led to the concept of an esophagobronchial reflex based on crosstalk at the nucleus tractus solitarius between esophageal and airway sensory neurons converging in this brainstem area [58].

This led to gastroesophageal reflux-associated cough, a cough-predominant phenotype of GERD, as a chronic airway inflammatory disease. Epithelial damage and airway inflammation in gastroesophageal reflux-associated cough patients suggest micro-aspiration, and the esophagobronchial reflex mediated by distal esophageal vagal afferents [136].

Chronic cough may result from GERD/extraesophageal reflux-induced airway inflammation and supra-esophageal pathology. Whether refluxate causes damage leading to extraesophageal reflux, needs to be acidic or merely contain pepsin, or whether neurogenic signaling leads to inflammation and subsequent symptoms remains unclear [134; 136].

In sum, GERD can directly affect the airways when gastric acid backflows into the esophagus, irritating the proximal esophagus and laryngopharyngeal areas, triggering the cough reflex to clear the airways. Gastric content can indirectly cause chronic cough by stimulating the distal esophagus, resulting in vagus nerve irritation and cough reflex sensitization. Airway reflux may comprise most cases of reflux-induced cough, its extraesophageal symptom hampering diagnosis based on symptoms alone [39].

Management

What diet and lifestyle modifications are recommended for all patients with known or suspected reflux-related chronic cough?

As discussed, the role of reflux, esophageal dysmotility, and aspiration in chronic cough is controversial. Studies suggest non-acidic reflux, both liquid and gaseous, may be an etiological factor. However, no tool reliably detects such reflux and diagnosis relies on clinical history supported by validated questionnaires (e.g., the HARQ). Moreover, the high prevalence of esophageal dysmotility in patients with chronic cough suggests esophagopharyngeal reflux rather than GERD may be the problem [10].

REFLUX INVESTIGATIONS IN PATIENTS WITH CHRONIC COUGH		
Investigation	**Description**	**Utility**
24-hour esophageal pH testing	A catheter is inserted nasally into the esophagus with two pH sensors for 24-hour measurement of proximal and distal acid reflux	Does not reliably predict response to PPI therapy
Barium meal	Radiographic test that visualizes the movement of barium liquid. Can detect structural and motility abnormalities of the esophagus, stomach, and duodenum.	May demonstrate a hiatal hernia and document the extent of non-acid reflux not identified on 24-hour pH testing
Manometry	A catheter is inserted to assess motility patterns by measuring the amplitude of contractile events in the esophagus and its sphincters	Impaired peristalsis is more prevalent in patients with chronic cough, consistent with symptoms of esophageal dysmotility
Impedance testing	Intraesophageal probes measure impedance and pH to record acid, weakly acidic, and non-acid reflux events	Non-acid refluxate may be important in chronic cough etiology, but impedance testing is not validated to investigate chronic cough
Upper GI endoscopy	Allows direct inspection of the upper GI tract and biopsy of stomach and duodenum	Often unrevealing; endoscopic evidence of GERD less common with atypical (e.g., chronic cough) vs. typical symptoms
Source: [19]		*Table 6*

Many of the signs and symptoms associated with chronic cough are explicable by reflux and aspiration, including voice change, nasal symptoms, and dysgeusia. Frequent chest infection bronchitis, even frank bronchiectasis, may be the consequence rather than the cause of cough via repeated aspiration. Unsurprisingly, following aspiration of GI contents there is a neutrophilic or eosinophilic inflammatory response that might be giving rise to asthmatic cough and mucus hypersecretion [10].

The 2016 ACCP clinical practice guideline for reflux-associated chronic cough suggests that esophageal manometry and pH-metry be performed in patients with suspected reflux cough refractory to a three-month antireflux trial and being evaluated for surgical management (antireflux or bariatric); or with strong clinical suspicion warranting diagnostic testing for gastroesophageal reflux (***Table 6***). Esophageal manometry assesses for major motility disorder. It involves placing the pH electrode 5 cm above the lower esophageal sphincter in the pH monitoring study after the patient is off PPIs for seven days and histamine H2-receptor antagonists for three days [83].

For overweight and obese patients, treatment of suspected reflux-cough should include diet change to promote weight loss. In all patients, recommended diet and lifestyle modifications include [6]:

- Eliminate coffee, tea, soda, other carbonated beverages, fish oil supplements, chocolate, mints, alcohol, and energy drinks, sports, or other drinks containing citric acid
- Consume no more than 45 grams of fat daily
- Avoid smoking and vaping
- Avoid exercising that markedly increases intra-abdominal pressure
- Elevate the head of the bed and avoid meals within three hours of bedtime

In patients with heartburn and regurgitation, PPIs, histamine H2-receptor antagonists, alginate, or antacid therapy is often sufficient to control these symptoms. Gastrointestinal symptoms respond within 4 to 8 weeks, but cough may take 12 weeks to improve [83]. PPI monotherapy is not recommended for chronic cough with solely extraesophageal symptoms, as it is unlikely to resolve the cough.

The ACCP suggests against antireflux surgery for patients with chronic cough patients with a major motility disorder and/or normal acid exposure time in the distal esophagus, as the procedural risks and lack of supporting evidence make the risk-benefit ratio unacceptable [83]. However, surgery may be considered for presumed reflux-cough in patients with normal peristalsis, abnormal esophageal acid exposure on pH-metry, and refractory to medical therapy.

PITFALLS IN THE MANAGEMENT OF CHRONIC COUGH
Upper Airway Cough Syndrome
Failing to recognize that upper airway cough syndrome (also asthma or GERD) can present as a cough-phlegm syndrome, misdiagnosed as chronic bronchitis. Assuming that all histamine H1 receptor antagonists (H1RAs) are the same. H1RAs without anticholinergic activity do not help nonallergic rhinitis conditions. Further, anticholinergic H1RAs may adversely affect memory, glaucoma, and prostate problems. Instead, consider ipratropium bromide nasal therapy. Failing to consider: • "Silent" upper airway cough syndrome when a patient does not sense a postnasal drip or realize their frequent throat clearing • Allergic rhinitis and recommend the avoidance of allergens because symptoms are perennial • Sinusitis because it is nonobvious • NSAID-exacerbated disease • The potentially beneficial role of upper respiratory endoscopy
Asthma
Failing to recognize that: • Asthma can present as cough alone (i.e., cough-variant asthma) • Inhaled medications may exacerbate cough • Positive methacholine challenge alone is not diagnostic of asthma
Nonasthmatic Eosinophilic Bronchitis
Failing to consider the diagnosis, occupational/environmental causes, or order the correct test
GERD
Failing to recognize that: • "Silent" reflux disease can be causal and that it may take two to three months of intensive treatment before cough starts to improve and five to six months to resolve • GERD can be worsened by comorbidities (e.g., obstructive sleep apnea) or their treatment (e.g., nitrates or calcium channel blockers for coronary artery disease, progesterone for hormone replacement) Assuming that: • Cough cannot be due to GERD because cough remains unchanged when gastrointestinal symptoms improve • Vocal cords' appearance can diagnose GERD, when inflammatory changes from coughing can mimic those of reflux Being unaware that acid suppression alone will not improve cough Failing to consider: • Non-acid reflux disease • The role of diet, intense exercise, and prokinetic therapy • Adequately treat co-existing causes of cough that perpetuate the cycle of cough and reflux because cough can provoke reflux
Triad of Upper Airway Cough Syndrome, Asthma, and GERD
Failing to consider that more than one condition may be contributing simultaneously to cough, or failing to consider additional contributing conditions because of another "obvious" cause (e.g., COPD) Failing to appreciate: • These chronic disorders cannot be cured and will periodically flare, especially with viral illness • When cough flares after a period of remission, re-evaluate as if a new problem • Asthma may become a problem when it was not before
Unsuspected Airway Diseases
Failing to perform bronchoscopy when chest x-ray and CT are normal. Transnasal route allows inspection of both upper and lower respiratory tracts. Failing to appreciate that prolonged IV therapy for suppurative airway disease may succeed when the same drug given orally failed
Source: [6; 80] *Table 7*

TREATABLE TRAITS AND THOROUGHNESS

The variable success in managing chronic cough may be due, in part, to guidelines or protocols not being implemented as planned (***Table 7***) [6; 80]. Failure to recognize the complexity of airway diseases can lead to suboptimal outcomes, as diseases with different endotypes can require different therapeutic strategies (precision medicine). Because the treatable traits approach is a label-free approach, it does not start on the assumption that the diagnosis (e.g., asthma, COPD) is well-established and clear, a situation that is not the case in many instances in clinical practice, particularly in primary care. This is a fundamental, but often overlooked, issue in the current guideline-directed management of airway diseases [14; 16].

Pulmonary and Extrapulmonary Traits as "Connected Comorbidities"

As discussed, the treatable traits approach encourages trans-diagnostic thinking about chronic cough and associated diseases to identify distinct endotypes and phenotypes within traditional diagnostic categories, as well as shared mechanisms across diagnostic boundaries. For example, asthma and severe chronic rhinosinusitis with nasal polyposis are frequently associated with other, coexisting type 2 inflammatory diseases, such as NSAID-exacerbated respiratory disease, allergic rhinitis, eosinophilic esophagitis, atopic dermatitis, and type 2 eosinophilic COPD [114]. Chronic rhinosinusitis with nasal polyposis has a 7% prevalence in patients with asthma, increasing to 40% in NSAIDs-exacerbated respiratory disease [138]. In predisposed subjects, a dysregulated type-2 inflammation can develop in epithelial barriers (e.g., airways, intestine, skin) in response to various antigens, such as allergens, micro-organisms, and pollutants. This dysregulated epithelial response leads to diseases such as asthma, rhinitis/rhinosinusitis, eosinophilic gastrointestinal disorders, and atopic dermatitis [95].

Allergens are not the only antigens that trigger inflammation. Rather than allergic disorders, type 2 disorders would be a more appropriate definition, also including non-allergic eosinophilic diseases such as nonasthmatic eosinophilic bronchitis, chronic rhinosinusitis, and eosinophilic disorders of the gastrointestinal tract [95].

Targeted biological therapies can also address conditions with shared type 2 pathophysiology. Biologics with FDA approval targeting type 2 inflammatory disease pathophysiology include dupilumab (anti-IL-4 and IL-13), omalizumab (anti-IgE), mepolizumab (anti-IL-5), and benralizumab (anti-IL-5R) [92]. Mepolizumab has proven effective in chronic rhinosinusitis with nasal polyposis and asthma with high eosinophil levels in sputum. Dual targeting of IL-4 and IL-13 by dupilumab has shown efficacy across chronic rhinosinusitis with nasal polyposis, asthma, eosinophilic esophagitis, and atopic dermatitis, and in uncontrolled COPD with high eosinophil counts [93]. Chronic cough, it should be stressed, has not been examined in any study of biological therapies.

The Argument for Thoroughness

The optimal clinical approach in chronic cough and refractory chronic cough continues to evolve. The ERS guideline suggests simplifying the diagnostic process to shorten a patient's journey to a diagnosis of refractory/unexplained chronic cough and limiting sequential empiric trials to two to four weeks unless responses are observed [10]. However, the 2023 BTS guideline and others argue for a more assertive approach to identify all treatable traits and maximize therapy response before diagnosing refractory/unexplained chronic cough [5; 78]. This would be the counterargument to the diagnostic-therapeutic empiric trials approach.

In a 2024 study, all 201 patients presenting to a cough center in 2018–2022 were prospectively studied. Refractory chronic cough (defined as persistent cough severity VAS ≥40 with little improvement after at least two treatment attempts) was diagnosed in 30.7% and unexplained chronic cough in 1.5% [78]. The authors suggest a thorough diagnostic algorithm, with frequent second-step investigations, enabled diagnoses of less common cough etiologies and the low (1.5%) unexplained chronic cough rate. As many therapeutic trials as necessary were engaged in order to target all identifiable treatable traits of chronic cough. Treatment followed a stepwise intensification of therapy and introduced add-on treatment of all cough causes, but this was time-consuming and related to difficulties in keeping patients' adherence. In routine practice, the authors usually recommend more than two therapeutic trials before diagnosing refractory chronic cough. When refractory/unexplained chronic cough is diagnosed, additional treatments should be initiated. These patients require nonpharmacologic and/or drug therapies with opioids, neuromodulators, or novel refractory chronic cough agents.

In a separate study conducted at a clinic in China, experts found that among 1,554 patients with chronic cough patients with negative chest x-rays, 58.8% were attributable to common causes, including nonasthmatic eosinophilic bronchitis (18.3%), cough-variant asthma (16.3%), gastroesophageal reflux-associated cough (13.2%), and upper airway cough syndrome (11.1%) [139]. In addition, 18.4% of cases were attributable to other causes: chronic bronchitis (6.1%), bronchiectasis (4.5%), atopic (4.4%), and postinfectious (3.5%) cough; 9.6% had chronic cough of unexplained etiology. Finally, 13.1% of cases were due to rare causes (e.g., bacterial bronchitis, somatic cough syndrome, diffuse panbronchiolitis, obstructive sleep apnea, and interstitial lung disease). These findings suggest that special examinations should be considered after excluding common causes of chronic cough.

It is important to remember that the workup to rule out refractory/unexplained chronic cough is not complete until bronchoscopy has been performed [6]. A study of bronchoscopy involving 54 patients with refractory/unexplained chronic cough with sputum production (more than 1 tbsp/day), atypical urge-to-cough sensations in chest, and unremarkable chest CT revealed bronchoalveolar neutrophilia in 84% and

excessive dynamic airway collapse in 31% [140]. Bronchoscopy influenced or changed the management in 89% of patients. Bronchoscopy findings in this specific population have rarely been described, and treatment strategies in these patients differ from typical refractory/unexplained chronic cough. Bronchoscopy provides high diagnostic value in refractory/unexplained chronic cough with mucus production, identifying specific treatable traits of neutrophilic airway inflammation and excessive dynamic airway collapse [140].

Another argument for moving away from the routine use of empiric therapeutic-diagnostic trials is to spare patients with chronic cough from exposure to minimally helpful or unhelpful medications with potentially adverse effects. For example, PPIs are recommended against for chronic cough in patients who lack classic GERD symptoms. Cumulative doses of PPIs dose-dependently increase the risk of developing hypomagnesemia and other side effects. Both hypomagnesemia and its consequent decrease in melatonin production can decrease lower esophageal sphincter tone and trigger a paradoxical iatrogenic cough. Rather than PPI dose escalation for partial responders, magnesium and melatonin supplementation is recommended to curtail side effects of long-term PPIs [104].

Oral corticosteroids, due to their substantial cumulative side effects, are now recommended only as a last resort in the most recent asthma treatment guidelines [141; 142]. Even occasional short courses of oral corticosteroids are associated with significant short-term and cumulative long-term adverse effects, with a pronounced dose-response. Short-term adverse effects of oral corticosteroids include sleep disturbance, increased appetite, reflux, mood changes, sepsis, pneumonia, and thromboembolism. As few as four to five lifetime courses of oral corticosteroids are associated with a significantly increased dose-dependent risk of diabetes, cataracts, heart failure, osteoporosis, and several other conditions [142].

TREATMENT OF REFRACTORY CHRONIC COUGH

What pharmacotherapeutic agents are recommended for the treatment of refractory or unexplained chronic cough?

Refractory and unexplained chronic cough are diagnoses of exclusion. For cases with no clear etiology after an extensive workup, or when guideline-based treatment improves the presumed underlying cause of coughing but not the chronic cough itself, cough hypersensitivity syndrome is the most likely explanation [39].

A variety of organizations have published guideline recommendations for the treatment of refractory and/or unexplained chronic cough (***Table 8***). The British Thoracic Society asserts that cough hypersensitivity is a treatable trait of many conditions and often the foremost problem in patients with chronic dry/unproductive cough [5]. However, there are currently no tools to positively identify cough hypersensitivity. If the condition does not improve with treatment of treatable traits, it is considered refractory chronic cough. In these patients, the most effective treatments are those addressing cough hypersensitivity and include low-dose morphine, gabapentin, and nonpharmacological therapy. In addition, novel therapies are in development, with P2X3 antagonists the most promising [5].

PHARMACOTHERAPY

Neuromodulators are centrally acting agents for refractory chronic cough that can downregulate the hypersensitive cough reflex to decrease coughing. Neuromodulators are first-line options for refractory chronic cough [39; 57]. However, some of the literature on neuromodulator use in patients with refractory chronic cough might seem counterintuitive.

Clinical trials of P2X3 antagonists have shown efficacy in reducing cough frequency in many patients with refractory/unexplained chronic cough, but the exact mechanisms underlying refractory/unexplained chronic cough remain poorly understood. Although data also suggest central mechanisms may be a key component in the pathophysiology of refractory/unexplained chronic cough, antitussive drug development has focused on peripheral targets [143].

Among patients with unexplained chronic cough started on amitriptyline and contacted by mail two to three years later, 64% had stopped the medication due to no improvement (40%) and/or side effects (48%). The most common side effects triggering treatment nonadherence were sedation (18%), dry mouth (18%), anxiety (8%), difficulty sleeping (8%), and dizziness (5%). Combining patients who continued and stopped amitriptyline, 53% reported cough improvement of at least 50%. There is some evidence that as treatment duration increases, amitriptyline efficacy may decrease [144].

Opioid Medications

The concept of chronic cough as a neuropathic condition, treated with neuromodulators, is not new. In 1856, Edward Smith described chronic cough as a "disease in itself" due to "irritability of the nerves" that could be treated with "morphia," 164 years before expert consensus in the European Respiratory Society chronic cough guidelines concluded the same, albeit for refractory chronic cough [10; 111]. Opioids are thought to exert antitussive effects through opioid receptors within inhibitory cortical descending pathways [59].

GUIDELINE RECOMMENDATIONS FOR NEUROMODULATOR TREATMENT OF REFRACTORY/UNEXPLAINED CHRONIC COUGH						
Drug	**Guideline Organization (Year)**					
	ACCP (2016)	**ERS (2020)**	**GRS (2020)[a]**	**FRS (2023)**	**BTS (2023)**	**NEURO-COUGH (2023)**
Low-dose morphine slow-release	Not reported[b]	Strong recommendation	Strong recommendation	Recommended: Grade B	Recommended	Recommended, very high consensus
Codeine	Not reported	Not recommended	Not reported	Not reported	Recommended against	Not reported
Gabapentin	Recommended	Conditional recommendation	Can be used	Recommended: Grade B	Recommended	Recommended, high consensus
Pregabalin	Not reported	Conditional recommendation	Can be used	Recommended: Grade B	Recommended	Not reported
Amitriptyline	Not reported	Not reported	Can be used	Recommended: Grade C	Not reported	Recommended, high consensus
Baclofen	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

[a]"Can be used" is a weaker endorsement than "recommendation" (i.e., "should be used").
[b]75% of expert panelists endorsed a recommendation of morphine, falling short of 80% required for inclusion; thus, morphine is neither recommended for nor against.
ACCP = American College of Chest Physicians; BTS = British Thoracic Society; ERS = European Respiratory Society; FRS = French-Speaking Society of Respiratory Diseases; GRS = German Respiratory Society; NEURO-COUGH = New Understanding in the treatment Of COUGH Clinical Research Collaboration; SR = sustained-release.

Source: [5; 10; 11; 12; 18; 86] *Table 8*

Codeine

Codeine is a weak opioid that is metabolized to morphine (5% to 10%) by the enzyme cytochrome P450 2D6 (CYP2D6) in the liver to produce its antitussive effects [145]. Codeine has long been used as an antitussive, but a minority of the population possess a genetic variation in CYP2D6 activity, with variable and unpredictable metabolism that increases unpleasant side effects and decreases efficacy. Codeine is now considered an unreliable antitussive and should not be used in chronic cough [5].

Low-Dose Morphine Slow-Release (SR)

Morphine is not affected by interindividual variability in CYP2D6 metabolism; thus, its biological effects are more predictable than codeine [146]. In the first positive results from a double-blind randomized controlled trial for any drug therapy of refractory chronic cough, morphine was selected to minimize the variability of codeine [25; 147]. This study compared twice-daily slow-release morphine 5 mg with placebo for four weeks, followed by four weeks of crossover to the alternate treatment. A three-month open-labeled extension of the randomized controlled trial allowed dose escalation to 10 mg twice per day if patients thought their cough was inadequately controlled [147].

The mean LCQ score significantly improved on morphine but not placebo, with significant improvement in physical, psychological, and social subdomains. A 40% reduction in daily cough scores was noted with morphine; placebo had no discernable effect over baseline. Of patients entering the extension, 67% opted for dose escalation and, after three months, had cough outcome improvements similar to 5-mg full-responder patients. Side-effects of constipation (40%) and drowsiness (25%) were tolerable; no patient dropped out from adverse events. Sedation, previously believed to explain the antitussive action of morphine, was transient, but the antitussive effect continued throughout the core and extension study phases [147].

The authors of this study state that side effects and dependence are obvious concerns with opioid therapy for what is a disabling but non-life-threatening condition. However, they note that the risk-benefit ratio makes low-dose slow-release morphine a credible therapeutic option in patients with refractory chronic cough for whom other treatments have failed. Comparisons

of similar therapeutic options were made with patients who require long-term oral corticosteroids for severe nonasthmatic eosinophilic bronchitis or cough-variant asthma with a consequently worse adverse event profile [147].

Another double-blind crossover study randomized previous morphine responders to slow-release morphine 5–10 mg twice daily or placebo. After five days, morphine reduced 24-hour cough frequency by 72% over placebo, including overnight (83%) and daytime (71%) cough frequency [148]. Morphine also significantly reduced noxious somatic sensations driving the urge to cough, suggesting this may be an important component of opioid modality in refractory chronic cough [149].

In a real-world effectiveness and tolerability study of long-term, low-dose opioids, 100 patients were prescribed twice daily slow-release morphine 5–10 mg (72%), oxycodone, or oxycodone/naloxone for a median 52 weeks for refractory/unexplained chronic cough. Median cough severity score (CSS, on a 0–10 scale) decreased from 8 pre-treatment to 4. In all, 60% had good-to-excellent response, while 25% had no response. Side effects (present in 38%) were most commonly constipation (25%), which was managed with dose reduction or constipation therapy; however, 15% stopped treatment due to side effect intolerance. Low-dose opioids improved long-term cough outcomes and were tolerated by most patients with refractory/unexplained chronic cough, but managing constipation allowed more patients to continue therapy [150].

Clinical experience with low-dose, slow-release morphine suggests that up to 50% to 60% of patients with refractory chronic cough obtain benefit [5; 59; 150]. Response dichotomizes into either a large effect on cough symptoms or no effect at all and is usually apparent within five days. The main side effect, constipation, can be managed with laxatives or adding oral low-dose naloxone. Once-daily dosing may be sufficient if cough symptoms are mainly troublesome during waking hours or overnight. Antitussive tolerance does not seem to develop. Unlike in severe chronic pain, there appears to be a dose ceiling for slow-release morphine of twice daily 10 mg, with no further antitussive effect beyond this. Concerns remain about misuse/addiction potential, and patients must be carefully monitored [5; 59]. As noted in a 2024 review, it is unclear why such low doses, compared with those used for analgesia, are effective in some patients with refractory chronic cough [25].

Gabapentinoids

Gabapentin and pregabalin are synthetic analogs of gamma-aminobutyric acid (GABA) that bind the α2δ subunit of voltage-gated calcium channels to block excitatory neurotransmitter release. Both were developed originally for epilepsy treatment and subsequently found to ameliorate chronic neuropathic pain, which is associated with central sensitization. The similar pathophysiologic mechanisms of chronic neuropathic pain and chronic cough suggested that gabapentin and pregabalin may also be beneficial in patients with refractory chronic cough [151].

Gabapentin (1,800 mg/day or the maximum tolerable dose) was compared with placebo for eight weeks in a double-blind randomized controlled trial of 62 patients with refractory chronic cough. Gabapentin significantly improved LCQ score over placebo by 1.8 points, and significantly reduced objective cough frequency and cough severity over placebo. Gabapentin response was greater in patients with symptoms of central sensitization (e.g., laryngeal paresthesia, allotussia, hypertussia). The onset of action of gabapentin took up to four weeks [152]. It was subsequently noted that cough frequency differed between gabapentin and placebo groups at baseline (45.3 vs. 68.8 coughs per hour) and was measured only for one hour at each assessment visit, making interpretation of cough frequency outcomes difficult [25; 146].

The European Respiratory Society suggests a trial of gabapentin or pregabalin in adults with chronic refractory cough.

(https://erj.ersjournals.com/content/55/1/1901136. Last accessed August 12, 2024.)

Strength of Recommendation/Level of Evidence: Conditional recommendation, low-quality evidence

An open-label randomized trial compared gabapentin (300 mg three times per day) to baclofen (20 mg three times per day), an antispasticity drug, in 234 patients with refractory gastroesophageal reflux-associated cough over nine weeks. Compared with baseline, gabapentin and baclofen similarly led to decreased cough symptom scores and patients with success for cough resolution (57.3% vs. 53.0%). Gabapentin led to lower side effect rates than baclofen of somnolence (20% vs. 35%) and dizziness (11% vs. 24%) [151]. In addition to other burdensome side effects, sudden discontinuation of baclofen can result in seizures [5].

In another study, twice daily pregabalin 75 mg was prescribed to 50 consecutive patients with refractory or unexplained chronic cough for three months. Pregabalin response, defined as LCQ total score improvement of ≥1.3, was attained by 56% of patients. Responders were more likely to have refractory (with underlying pulmonary disease) than unexplained chronic cough, and on average were more symptomatic at baseline. There was no information on side effects or dropout [153].

In another study, 40 patients with refractory chronic cough were randomized to speech pathology treatment plus pregabalin 300 mg/day or speech pathology treatment plus placebo for four weeks. Compared with the placebo group, those who received speech pathology treatment/pregabalin experienced a statistically significant improvement [154]. However, CNS adverse effects (e.g., dizziness, disorientation, confusion, fatigue, blurred vision) were common and sometimes intolerable. The effects of pregabalin on 24-hour cough frequency outcome were non-significant [146].

Because gabapentinoids have beneficial effects on anxiety, improvements in mood may contribute to the apparent benefit or changes in symptom perception or cough intensity. Side effects are common, wide ranging, and can be difficult for patients to tolerate. Slow dose escalation may help minimize this, and maximal doses may not be needed to afford some improvement in cough. Gabapentin and pregabalin may have abuse potential in susceptible patients [5].

Gabapentin should be started at a low dose (e.g., 100 mg three times per day) and titrated up to a maximum dose (600 mg three times per day), depending on clinical effects and tolerability. The usual starting dose of pregabalin for chronic cough is 25 mg twice daily, with increases in increments to a maximum 75 mg twice daily. Patients should be reassessed during dose titration and therapy stopped if there are significant side effects or inadequate response to treatment [5].

In clinical experience, the minority of patients who achieve cough suppression often do so at the expense of intolerable adverse effects, usually sedation [57]. Among 38 patients prescribed gabapentin (maximum: 1,800 mg per day) or pregabalin (maximum: 300 mg per day) for refractory chronic cough, 24% developed immediate intolerable side effects and 37% tolerated the drugs but had no response and stopped the medication. Among the 39% with an initial favorable response, 18% eventually developed intolerable side effects and 21% were able to continue with therapy long-term. The most common side effect was drowsiness/sedation. In real-world practice, gabapentinoids are effective in a subgroup of patients with refractory chronic cough, but side effects may outweigh their potential benefits, which were intolerable for 42% of patients [155].

Tricyclic Antidepressants

Amitriptyline and nortriptyline are tricyclic antidepressants with a broad range of pharmacologic actions effecting adrenergic, serotonergic, muscarinic, and histaminergic systems. Amitriptyline is also used in chronic neuropathic pain (e.g., migraine, postherpetic neuralgia, painful diabetic neuropathy) and has been suggested to be effective in the treatment of chronic cough, with anticholinergic properties thought to underlie the antitussive effect [57; 156]. However, clinical experience with amitriptyline in refractory chronic cough suggests more limited value [5].

In a small randomized trial of patients attending an otolaryngology clinic with postviral refractory chronic cough, amitriptyline 10 mg per day was compared with codeine 10 mg/guaifenesin 100 mg combined in a syrup taken every six hours. The majority of patients reported a 75% to 100% improvement in cough with amitriptyline, while most reported no improvement with codeine/guaifenesin. Compared with the control arm, amitriptyline was significantly associated with a response greater than 50% [157]. In a randomized controlled trial of patients with chronic pharyngolaryngeal neuropathy, 67% had subjective improvement with amitriptyline (up to 50 mg/day), compared with 44% with placebo. The mean Voice Handicap Index-10 (VHI-10) score worsened with amitriptyline but was unchanged with placebo. Attrition over the eight-week trial was 40% [158].

Nortriptyline was studied in 42 patients with neurogenic chronic cough, of whom 45% discontinued nortriptyline due to side effect intolerance or lack of response. The average time to clinical response was 5.5 months. The average minimum effective dose was 21 mg per day in responders. Laryngeal asymmetry was present in 85.7% of all patients. Side effects included sedation, xerostomia, and anxiety. The intolerability was surprising, because nortriptyline is both a metabolite of amitriptyline and reported to be better tolerated [159].

Pharmacotherapy for Chronic Cough in Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is a chronic, progressive, and invariably fatal fibrotic lung disease, and 85% of patients with idiopathic pulmonary fibrosis experience cough, a distressing symptom associated with rapid disease progression. Available treatments for idiopathic pulmonary fibrosis slow disease progression but do not improve symptoms or quality of life. Thalidomide benefitted idiopathic pulmonary fibrosis cough in one randomized controlled trial, but its side effect profile renders it practically useless, as only 20% of patients were able to tolerate it [125]. Worse still, the potentially severe adverse effect of peripheral neuropathy suggests it may damage sensory nerves (vagal afferents). Thalidomide should not be considered even as second-line therapy for idiopathic pulmonary fibrosis cough until further evaluation of the benefit/risk ratio has been undertaken [160].

Although studies on refractory chronic cough can help inform the treatment of idiopathic pulmonary fibrosis cough, the biological mechanisms that contribute to cough probably differ in these conditions, as evidenced by the contrasting results with gefapixant, a P2X3 receptor antagonist, in refractory chronic cough (positive findings) and idiopathic pulmonary fibrosis cough (negative findings) [161].

Nalbuphine

Nalbuphine extended-release (ER) is an opioid agonist-antagonist. In a double-blind randomized controlled trial of patients with idiopathic pulmonary fibrosis and chronic cough, nalbuphine ER tablets (titrated up to 162 mg twice daily) led to 75.1% reduction in daytime objective cough frequency, compared with 22.6% with placebo, a 50.8% placebo-adjusted reduction in 24-hour cough frequency, and similar improvements in patient reported outcomes [162]. Nalbuphine ER was the first therapy to show robust effects on chronic cough in idiopathic pulmonary fibrosis [25]. However, nalbuphine side effects of nausea (42.1%), fatigue (31.6%), constipation (28.9%), and dizziness (26.3%) led to a 24% dropout during the drug initiation phase, partially attributed to the inflexible forced-titration study design [162].

Low-Dose Morphine SR

In a multicenter randomized controlled trial of patients with idiopathic pulmonary fibrosis and chronic cough, low-dose, slow-release morphine (5 mg twice daily) reduced objective awake cough frequency by 39.4% over placebo, and all cough-related patient-reported outcomes remained significantly improved when adjusted for placebo. Morphine side effects of nausea (14%) and constipation (21%) resulted in only one participant discontinuing morphine, indicating tolerability for these patients. The authors note that the safety assessments during study visits were reassuring and there appeared to be no changes in mood or excessive fatigue with morphine [161]. The authors advocate for rapid implementation in clinical practice due to the well-established safety profile and worldwide availability [163].

A 2024 study reported variable effectiveness of slow-release morphine (8–32 mg per day) in reducing breathlessness in patients with COPD. But, it provided reassuring safety data by observing no evidence of harm and no worsening of subjective daytime sleepiness, alertness, or sleep quality at one and four weeks in these severely ill patients [164].

INVESTIGATIONAL PHARMACOTHERAPIES

Low-dose, slow-release morphine has the strongest observational and empirical evidence of antitussive benefit in refractory chronic cough of any commercially available (although off-label) medication and may be used safely in this population when patients are carefully screened and monitored. Because as many as 50% of patients with refractory chronic cough have no response to low-dose morphine and with substantial restrictions on opioid prescribing in the United States, effective peripherally acting antitussives are an urgent priority for investigators.

P2X3 Receptor Antagonists

P2X3 receptors form ion channels containing ATP-binding sites. In the lungs and airway, ATP activates P2X3 receptors localized on vagal sensory nerve terminals, resulting in bronchoconstriction, cough, and localized release of inflammatory neuropeptides [165].

A breakthrough occurred when gefapixant, a P2X3 receptor antagonist, demonstrated a dramatic reduction in chronic cough. Other P2X3 antagonists confirmed the efficacy of this drug class in refractory chronic cough. The endogenous ligand for P2X3 is ATP. Epithelial damage is believed to release ATP. Evidence suggests that ATP largely mediates peripheral hypersensitivity; therefore, gefapixant is peripherally acting in refractory chronic cough [166].

P2X3 receptors are ion channels found on sensory afferent nerve fibers, activated by ATP. In preclinical studies, vagal C fibers, including those thought to be important in mediating cough, have been shown to express P2X3 and P2X2. At present, it is unclear whether ATP concentrations are elevated or P2X3 receptor expression increased in the airways of patients with refractory chronic cough, or how antagonism of P2X3 plays a role in reducing coughing to a range of chemical irritants, temperature changes, and mechanical stimuli. Nonetheless, in clinical trials, P2X3 receptor antagonism has provided robust reductions in cough frequency and patient-reported outcomes [25].

Gefapixant

The first novel therapy to have significant effects in patients with refractory chronic cough was gefapixant, a first-in-class P2X3 antagonist that was originally planned to be developed as an analgesic. Gefapixant has become the first therapeutic to undergo systematic development as a treatment for refractory chronic cough following unprecedented reductions in cough frequency.

In a landmark study, twice daily gefapixant 600 mg showed remarkable therapeutic effects in patients with refractory chronic cough [167]. Objective 24-hour cough frequency was reduced 74% compared with placebo, and daytime cough severity VAS score and CQLQ score reduced by −25.6 and −9.2, respectively. However, another important finding was that virtually all treated patients reported ageusia, or loss of taste, and 24% withdrew because of the adverse effect. These taste side effects are likely attributable to the inhibition of P2X2/3 channels on the nerve fibers innervating the taste buds by high-dose gefapixant [146].

Subsequent studies suggest that antitussive effects are retained at much lower doses (30–50 mg twice daily), at which taste was altered rather than lost and hence the therapy was better tolerated. Larger multi-center parallel group studies were performed in the UK and the United States followed by the first-ever global phase 3 trials of an antitussive treatment for refractory chronic cough, which reported positive findings over placebo for a 45-mg twice daily dose [25].

Eliapixant and Filapixant

Following the taste side effects reported for gefapixant, more selective P2X3 antagonists were evaluated for the treatment of refractory chronic cough; however, there was some uncertainty about whether effects at both P2X3 and P2X2/3 channels were both contributing to antitussive efficacy and hence whether more selective agents would have similar efficacy. Eliapixant and filapixant both demonstrated efficacy in dose-ranging studies, but eliapixant appeared to cause less taste disturbance (up to 21% of patients) and was therefore progressed to a phase 2b parallel trial. Although this trial reported positive findings, a small number of cases of liver toxicity prevented further development of this therapy for refractory chronic cough [25].

Sivopixant

Another more selective P2X3 antagonist, sivopixant, exhibited promising findings in a single-dose crossover study, very similar in design to the first gefapixant study. The reduction in daytime cough frequency of 32% over placebo (the primary endpoint) was not quite statistically significant, but taste adverse effects were only reported in 6.4% of patients. In a follow-up, multicenter parallel group study assessing a range of doses for four weeks, no dose of sivopixant could be discriminated from the very large placebo effect—there was 60% placebo reduction in cough frequency from baseline. The largest absolute change in cough frequency was observed for the highest dose (300 mg), but 30% of patients reported taste adverse effects. No further studies of sivopixant in refractory chronic cough have been planned [25].

Camlipixant

Finally, thought to be the most selective P2X3 antagonist, camlipixant is the second compound in this class to be evaluated in phase 3 trials. The first double-blind randomized controlled crossover trial of camlipixant studied escalating doses from 25 mg to 200 mg versus matched placebo. Although the primary endpoint of awake cough frequency did not reach statistical significance, preplanned subgroup analysis in patients with a cough frequency of at least 20 coughs per hour (80% of patients) and those with greater than the median cough frequency (≥32 coughs per hour, 50% of patients) exhibited significant improvements versus placebo for all doses tested. This preplanned analysis was based on observations from several of the gefapixant studies that suggested P2X3 antagonism was most efficacious in patients with the highest baseline cough frequency [25].

In post-hoc analysis of a phase 2a study, among patients who reported cough-related urinary incontinence at baseline, 11%, 15%, and 21% of those treated with 12.5 mg, 50 mg, and 200 mg camlipixant, respectively, reported no cough-related urinary incontinence at day 29 (compared with 3% with placebo) [168]. As of 2024, camlipixant is being evaluated in two large-scale phase 3 studies, again in patients selected for higher cough frequencies [25].

Other Novel Antitussives Under Investigation

The studies completed to date investigating P2X3 antagonists have typically found that between one-quarter and one-third of patients do not experience the 30% reduction in cough frequency thought to be the meaningful clinical threshold, suggesting some heterogeneity in the mechanisms underlying refractory chronic cough. Furthermore, patients with less frequent/severe coughing than those recruited to these trials may not benefit from treatments interrupting the ATP-P2X3 axis. Therefore, treatments with alternative modes of action are required to optimally manage patients with refractory chronic cough [25].

Sodium Channel Blockade

Lidocaine non-selectively blocks voltage-gated sodium channels important in the initiation of action potentials and their conduction and is a local anesthetic agent in routine topical use to reduce coughing during bronchoscopy. Case reports and case series have also described the use of nebulized lidocaine as an antitussive to treat refractory chronic cough [169].

In a three-way crossover study of single-dose lidocaine in refractory chronic cough, lidocaine throat spray reduced coughing by about 50% and was more effective than nebulized lidocaine, probably because nebulization into the lower airways has an irritant effect and evokes coughing initially [169]. The antitussive effects of lidocaine spray are relatively short lived and also associated with numbness in the mouth and lips, preventing patients from safely eating after treatment. Efforts have been made to develop similar therapies with a longer duration of action and without loss of sensation [25].

A novel approach to sodium channel blockade has been developed using a compound that is only active in blocking sodium channels after entering neurons via large-pore ion channels, such as P2X3 channels. As of 2024, a phase 2a clinical trial has been performed but the results are not yet published.

TRPM8 Agonism

Activation of TRPM8 ion channels produces cooling sensations. One new therapy has used an orally dissolving tablet containing a TRPM8 agonist (AX-8) placed on the back of the tongue to act as a counter irritant to the sensations of throat irritation reported by many patients with refractory chronic cough. In a randomized controlled trial, AX-8 reduced cough frequency, but not significantly over eight hours, the duration of action suggested by a previous open-label study. However, the effect was significant over four hours and exaggerated in those patients reporting greater throat discomfort, consistent with the proposed mechanism of action. Further studies in this subgroup of patients are hoped to confirm efficacy [25].

On day 1, AX-8 reduced cough frequency within 15 minutes and more than placebo over two and four hours, but not eight hours. In participants with baseline throat discomfort, reduction in cough frequency was significant over 24 hours, with a maximum reduction compared to placebo of 43% over two hours. Over 14 days, AX-8 significantly improved patient-reported outcomes and the safety profile was good with no serious adverse events. This suggests that TRPM8 agonism has potential for control of refractory/unexplained chronic cough as an alternative or adjunct to other therapies, especially in those patients complaining of cough driven by throat sensations [170].

NK-1 Antagonism

Following a positive study testing aprepitant as a cough treatment in patients with lung cancer, there has been interest in the potential antitussive effects of centrally acting neurokinin-1 (NK-1) antagonists. Following a negative trial in refractory chronic cough, a double-blind randomized controlled trial is in progress testing the effects of orvepitant in patients with cough associated with idiopathic pulmonary fibrosis [25].

NONPHARMACOLOGIC THERAPY

Speech and Language Therapy

Speech and language therapy techniques were first described as improving chronic cough in a randomized controlled trial in 87 patients with refractory chronic cough. The intervention appeared to have positive impact on cough, voice, throat symptoms, and symptom limitation after four therapy sessions over two months. Another study investigated a similar intervention delivered by speech and language therapists and physiotherapists. Compared with sham therapy, LCQ score improved by 1.5 points. Cough frequency improved by 40% more than in the sham-treated arm at four weeks and seemed to be maintained at three months. No larger-scale trials have been completed [25].

Speech and language therapy is a complex intervention, comprising components of education, cough suppression techniques, vocal hygiene, and psychoeducational counseling. Thus, it is difficult to standardize the intervention, and it is not clear whether all or just some of the components are essential for efficacy. In practice, the therapy seems to be most effective when delivered by experienced therapists, who may not be widely available. There is also a question about the durability of the effects over longer timescales when patients may not continue to practice the techniques [25].

The European Respiratory Society suggests a trial of cough control therapy (physiotherapy/speech and language therapy) in adult patients with chronic cough. (https://erj.ersjournals.com/content/55/1/1901136. Last accessed August 12, 2024.)

Strength of Recommendation/Level of Evidence: Conditional recommendation, moderate-quality evidence

The speech and language therapy approach to the management of chronic cough involves four steps: education, vocal hygiene, cough control/suppression training, and psychoeducational counseling [19].

Education

Patients are provided education on the biology of coughing, chronic cough, and cough hypersensitivity. The negative effects of repeated coughing and throat clearing are explained [19].

Vocal Hygiene

Vocal and laryngeal hygiene and hydration are advised with a reduction in caffeine and alcohol intake. Nasal breathing with nasal douching may be recommended with nasal steam inhalation [19].

Cough Control/Suppression Training

Following identification of patient cough triggers, patients are taught a range of suppression strategies, including forced/dry swallow, sipping water, chewing gum, or sucking non-medicated sweets. Breathing pattern re-education is used to promote relaxed abdominal breathing while inhaling through the nose [19].

Psychoeducational Counseling

Behavior modification is used to reduce over-awareness of the need to cough and facilitate an individual's internalization of control over their cough and to help manage stress and anxiety [19].

Local Injection Therapies

The experience of superior laryngeal nerve block by the injection of local anesthetic agents and corticosteroids has been described retrospectively following implementation in several clinics. In 2024, a small single-blind placebo-controlled study was performed comparing this treatment in 10 patients injected with active treatment and 7 with placebo, finding improvements in cough VAS and LCQ scores. Transient sensations of globus (lump in the throat) and soreness at the site of inject were the main adverse effects. Laryngeal botulinum toxin injections have also been reported to produce improvements in series of patients in clinical care, but no controlled studies have been performed. The broad safety of these interventions and duration of any effect currently remains unclear [25].

CONCLUSION

Chronic cough affects roughly 10% of adults in the United States [32]. These individuals can cough hundreds to thousands of times every day, often with uncontrollable bouts of coughing triggered by laughing, speaking, or changes in ambient temperature. This can continue for many years or decades, leading to substantial physical and emotional symptoms, including fatigue, urinary incontinence, cough syncope, dysphonia, depression, anxiety, embarrassment, social isolation, and severely diminished quality of life [28; 40; 64].

In 20% to 59% of patients with chronic cough, coughing persists despite extensive guideline-recommended evaluation and treatment of comorbidities or an underlying cause of cough cannot be identified. In these cases, a diagnosis of refractory or unexplained chronic cough is rendered [7; 36].

Chronic cough is a distinct pathologic entity (cough hypersensitivity syndrome) that develops when repetitive activation of airway cough receptors (typically by inflammatory mediators) induces neuroplastic changes, resulting in peripheral and central sensitization with symptoms of allotussia, hypertussia, and/or laryngeal paresthesia [3; 19; 20]. Hypersensitivity of vagal afferent neurons in the airways and their central projections, and deterioration in cortical inhibitory control of cough, explain the chronicity characteristics of this condition [33; 78].

According to current best evidence, clinical management of patients with chronic cough requires that clinicians perform thorough history, physical examination, and diagnostic testing to identify any potential underlying causes, with asthma, COPD, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and GERD the top diagnoses to consider. After assessment is complete, clinicians should treat any identified airway and esophageal conditions according to practice guidelines. As part of the treatment approach, behavioral treatable traits, including cigarette smoking, use of ACE inhibitors and NSAIDs, poor inhaler technique (when relevant), and treatment adherence in general should be identified and addressed [5; 6; 10; 18; 24; 25; 79; 171].

It is important to recognize that cough hypersensitivity syndrome is present when cough persists despite etiologically based treatment or no etiology can be identified. Clinicians can make a diagnosis of refractory or unexplained chronic cough and refocus management to downregulating a hyper-reactive cough reflex using commercially available medication prescribed off-label and cough-specific speech and language therapy [5; 6; 10; 18; 24; 25; 79; 171].

Despite showing the best effectiveness, safety, and tolerability of commercially available medications evaluated in patients with refractory/unexplained chronic cough patients and despite recommended by international clinical practice guidelines, use of low-dose, slow-release morphine may be untenable or unrealistic. In light of this fact, gabapentin, pregabalin, and amitriptyline remain options for effective pharmacotherapy. Clinicians should also stay informed about possible FDA approval of gafapixant, the first-ever drug approved for refractory/unexplained chronic cough in several other countries, and about phase 3 trials of campilixant. Approval of these agents could expand the treatment options for these patients and potentially improve patient quality of life.

Customer Information and Evaluation are located on pages 79–80.

Pathophysiology: The Hepatobiliary System

Includes 3 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses in all practice settings.

Course Objective
As health care becomes more complex, it is essential that the theoretical concepts of the basis of illness (pathophysiology) be well understood. The purpose of this course is to reinforce the scientific rationales for the interventions nurses perform and the decisions nurses make as patients move through the ever-changing struggle with their illness.

Learning Objectives
Upon completion of this course, you should be able to:

1. Identify and describe the anatomical structure of the liver.
2. Explain the liver's functions, integrating how these processes inter-relate with the hepatic and biliary systems.
3. Describe the anatomical location and structure and regulatory mechanisms of the gallbladder.
4. Discuss the pathophysiologic effects of hepatobiliary dysfunction, including how these conditions impact overall health and clinical management.
5. Review the impact of hepatobiliary dysfunction on the integumentary, cardiovascular, and neurologic systems.
6. Analyze how psychosocial and lifestyle factors influence the risk and progression of hepatobiliary disorders.
7. Conduct a comprehensive nursing assessment by effectively gathering and analyzing subjective and objective data related to hepatobiliary function.
8. Outline and interpret various diagnostic studies for hepatobiliary disorders, including the purpose, procedure, and nursing implications for advanced diagnostic tests.
9. Identify and formulate nursing diagnoses for patients with hepatic or biliary dysfunction based on comprehensive assessments.
10. Outline a comprehensive nursing care plan for patients with hepatobiliary dysfunction.
11. Differentiate between congenital disorders of the hepatic and biliary systems, specifically Gilbert syndrome and Alagille syndrome.
12. Discuss cirrhosis, including demonstrating an ability to apply appropriate therapeutic measures for managing complications and execute specific nursing interventions.
13. Differentiate between various forms of alcohol-induced liver disease.
14. Evaluate the role of metabolic dysfunction in the development of metabolic dysfunction-associated steatotic liver disease (MASLD).
15. Compare and contrast primary and secondary biliary cholangitis, including approaches to management.
16. Identify and differentiate between various infectious and inflammatory disorders of the hepatobiliary system.
17. Describe the various neoplastic and obstructive disorders affecting the hepatobiliary system.
18. Outline the key criteria for liver transplantation candidacy and the processes involved in donor organ selection and transplantation.

Faculty
Jane C. Norman, RN, MSN, CNE, PhD, received her undergraduate education at the University of Tennessee, Knoxville campus. There she completed a double major in Sociology and English. She completed an Associate of Science in Nursing at the University of Tennessee, Nashville campus and began her nursing career at Vanderbilt University Medical Center. Jane received her Masters in Medical-Surgical Nursing from Vanderbilt University. In 1978, she took her first faculty position and served as program director for an associate degree program. (A complete biography appears at the end of this course.)

Mary Franks, MSN, APRN, FNP-C, is a board-certified Family Nurse Practitioner and NetCE Nurse Planner. She works as a Nurse Division Planner for NetCE and a per diem nurse practitioner in urgent care in Central Illinois. Mary graduated with her Associate's degree in nursing from Carl Sandburg College, her BSN from OSF Saint Francis Medical Center College of Nursing in 2013, and her MSN with a focus on nursing education from Chamberlain University in 2017. (A complete biography appears at the end of this course.)

Faculty Disclosure

Contributing faculty, Jane C. Norman, RN, MSN, CNE, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, Mary Franks, MSN, APRN, FNP-C, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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NetCE designates this continuing education activity for 3 pharmacotherapeutic/pharmacology contact hours.

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This course represents an educational model that promotes the importance of learning objectives and individualized learning. Study questions will appear throughout the course to create a link between the learning objectives and the supporting text.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the study questions and course material for better application to your daily practice.

INTRODUCTION

The liver, the gallbladder, and the exocrine pancreas are classified as accessory organs of the gastrointestinal tract and digestion. They introduce digestive hormones and enzymes into the alimentary canal, ensuring that the nutrients critical to life can be absorbed selectively by the small intestines into the bloodstream. In addition to producing digestive secretions, the liver and the pancreas have other important functions. The exocrine pancreas, for example, supplies the insulin and glucagon needed in cell metabolism, whereas the liver synthesizes glucose, plasma proteins, and blood clotting factors and is responsible for the degradation and elimination of drugs and hormones, among other functions. The liver and gallbladder perform several regulatory functions essential to the maintenance of homeostasis. The liver synthesizes a number of substances, including coagulation factors that are vital to life. The gallbladder plays an important role in the digestive process, in particular the digestion of fats. Although the human body can survive the loss of the gallbladder, survival without a liver is not possible [1; 2]. This course focuses on functions and disorders of the liver, the biliary tract, and the gallbladder.

STRUCTURAL AND FUNCTIONAL INTER-RELATIONSHIPS

The hepatic and biliary systems are both structurally and functionally inter-related. The liver, the largest of the internal organs, performs the following functions [3]:

- Storage and filtration of blood (a vascular function)
- Production of bile (a regulatory function)
- Removal of bilirubin from the body (an excretory function)
- Metabolism of carbohydrates, fats, and protein (a metabolic function)
- Storage of vitamins A, D, and B12
- Synthesis of coagulation factors
- Detoxification of chemicals

The principal function of the gallbladder is to store and release bile [3].

STRUCTURE OF THE LIVER

What are the major regions of the liver?

The normal liver of an adult weights about 1,500 g. The wedge-shaped organ lies in the upper right quadrant of the abdominal cavity, where it is protected by the rib cage. The superior surface underlies the diaphragm. The posterior and inferior surfaces together are generally referred to as the visceral surface. The right visceral surface is in contact with portions of the colon, the kidneys, the adrenal glands, and the duodenum; the left visceral surface is bordered by the stomach and spleen [3; 4].

The liver is divided into two major regions, the right and left lobes, separated by fissures on the inferior surface on the liver. On the posterior and inferior surfaces of the right lobe are two smaller lobes: the caudate and quadrate lobes. The gallbladder and the inferior vena cava lie in two shallow fossae that parallel the fissures. Veins, arteries, nerves, and lymphatic vessels enter and leave the liver through a space between the caudate and quadrate lobes [3; 4].

Except for the so-called bare area, which rests against the diaphragm, the liver is covered by visceral peritoneum. A thin layer of connective tissue extends into each lobe to divide the liver into 50,000–100,000 liver lobules. These tiny structures, a few millimeters in length and 1–2 mm in diameter, are the functional units of the liver [3; 4].

The Functional Liver Lobule

Each liver lobule is composed of plate like "spokes" of hepatic cells that radiate from a "hub" or central vein that passes through the connective tissue between lobules. The central veins are branches of the portal vein that, together with the portal artery, furnish the blood supply of the liver. Bile is manufactured in the hepatic plates, each of which is generally two cells thick. Tiny bile canaliculi, or bile channels, lying between the hepatic plates carry the bile to bile ducts. Like tributaries forming ever larger streams, the bile ducts merge to form larger ducts. Eventually, they form two hepatic ducts, one from the right lobe and one from the left. These in turn join to form a single hepatic duct that merges with the cystic duct to form the common bile duct. Bile manufactured by the liver, together with bile stored and later secreted by the gallbladder, leaves the hepatic-biliary system via the common bile duct [5].

The septa between lobules contain venules and arterioles, both of which drain into the hepatic sinusoids, where venous and arterial blood mingle. This mingling is related to the detoxifying and metabolic functions of the hepatic system. Plasma, including proteins, can diffuse out of the blood. For example, nutritive or toxic substances carried from the intestine in the blood diffuse through the epithelial lining of the sinusoids into the hepatic cells, where they are metabolized, stored, or altered. The sinusoids are also lined by Kupffer cells, phagocytic cells that remove bacteria and other foreign substances from blood that passes through the liver [5].

Hepatic Circulation

The liver is richly supplied with both arterial and venous blood. Each minute, approximately 1,100 mL arrives from the hepatic portal vein and 400 mL from the hepatic artery to mix in the sinusoids before returning to the heart via the inferior vena cava. Portal venous blood coming from the intestines has a low concentration of oxygen but a high concentration of substances absorbed by the intestine during digestion. Blood

coming from the hepatic artery is high in oxygen but low in nutrients. The pressure of blood in the portal and haptic veins is low, allowing easy diffusion of nutrients and other substances along the concentration gradients. Oxygen-rich blood from the hepatic artery maintains the integrity of the liver; if perfusion is absent or diminished, necrosis of hepatic cells will occur [5].

Arterial and venous vessels, bile ducts, and lymphatic vessels travel together through the liver in so-called portal tracts. The direction of flow is from the portal tracts through the sinusoids and into the central veins of the liver lobules. Thus, oxygen and nutrient supply is richest in the hepatic cells nearest the portal tracts and poorest near the central veins. The cells adjacent to the central veins, due to their relatively poor nutritional state, are more susceptible to damage from circulatory disturbances (e.g., shock, heart failure) and more vulnerable to toxins than the outermost cells [5].

FUNCTIONS OF THE LIVER

What are the functions of the liver?

As discussed, the hepatic system has vascular, secretory, and metabolic functions. It stores some vitamins and iron, detoxifies chemicals, and forms substances necessary for the coagulation of blood [5; 6].

Vascular Functions

The liver is capable of storing a considerable quantity of blood, the amount depending on the pressure relationships in the arteries and veins. If pressure in the hepatic veins increases by a few millimeters of mercury (e.g., in the presence of congestive heart failure, cirrhosis, or hepatic congestion), as much as 300–400 mL of blood may be stored. If hemorrhage occurs anywhere in the body, the liver releases this stored blood into the circulatory system to maintain circulatory volume [6].

The phagocytic Kupffer cells lining the sinusoids normally remove 99% to 100% of bacteria from blood entering the liver. Kupffer cells multiply in response to increased levels of foreign particles in the blood. Because blood entering the liver through the portal vein contains intestinal bacteria, the Kupffer cells play an important role in the body's defense against infection. Any condition that damages these cells or inhibits their replication increases the body's susceptibility to infection [6].

Secretory Functions

The hepatic cells of each liver lobule continually secrete small amounts of bile, a thick, greenish-yellow, slightly alkaline fluid. When first secreted from the liver through the canaliculi, bile is composed of water, bile salts, bilirubin, cholesterol, fatty acids, and lecithin as well as sodium, potassium, calcium, chloride, and bicarbonate ions [5; 6].

Bile is concentrated in the gallbladder, which contracts during digestion to send it into the duodenum, where it functions as kind of "biological detergent" to emulsify fat particles. The bile salts decrease the surface tension of fat particles so the agitation of the intestinal tract can break them into small globules easily acted upon by digestive enzymes. Lecithin acts similarly. Fat is digested much more slowly if bile is not present [5; 6].

Bile salts also improve absorption of lipids. The salts combine with fatty acids and monoglycerides to form small complexes called micelles. The ion charges provided by the bile salts enhance diffusion of the micelles across the intestinal mucosa into the bloodstream [5; 6].

If absorption of fats is diminished because of absence of bile, vitamins A, D, E, and K, which are fat-soluble, cannot be absorbed. Bile salts are "recycled" from 15 to 20 times in a process known as enterohepatic circulation. An estimated 90% to 95% of bile salts secreted are reabsorbed in the distal ileum and carried in the portal vein back to the hepatic cells, which reabsorb and then resecrete them [5; 6].

Excretory Functions

Bilirubin (bile pigment), a major waste product of hemoglobin metabolism, is excreted by the liver. Normally, erythrocytes have a lifespan of about 120 days. They are then broken down by the reticuloendothelial cells, and the iron (heme) from the worn-out red cells is conserved for reuse in the synthesis of fresh hemoglobin. The remaining iron-free pigment is free (unconjugated) bilirubin, which is continually present in the bloodstream in small quantities. As blood passes through the liver, unconjugated bilirubin is removed. It is then combined (conjugated) with other substances and excreted via the bile ducts; a small amount of conjugated bilirubin returns to the blood [1; 7].

Conjugated bilirubin is more soluble and less toxic than unconjugated bilirubin. In the intestines, conjugated bilirubin is converted into a highly soluble substance called urobilinogen, which is excreted primarily in the feces in an oxidized form known as stercobilin. About 5% of urobilinogen is absorbed into the bloodstream and excreted via the kidneys in an oxidized form called urobilin. Because stercobilin gives feces their brownish color, clay-colored stools are a classic sign of biliary tract abnormalities [1; 7].

Metabolic Functions

Carbohydrate Metabolism

The liver plays a major role in carbohydrate metabolism. One aspect of this role is a glucose buffer function that contributes to the maintenance of normal blood sugar levels. The liver can remove excess glucose from the blood, store it as glycogen, and reconvert and release it as glucose in response to hypoglycemia. If blood glucose concentrations fall and glycogen is not available, the liver can convert proteins or amino acids to glucose, a process known as gluconeogenesis. The liver is also capable of converting galactose to glucose [1; 2].

Fat (Lipid) Metabolism

Synthesis of fat from carbohydrates and proteins occurs primarily in the liver. The lipoprotein produced in this process is transported in the bloodstream to the body's adipose tissue or storage. The liver is also capable of rapid metabolism of ingested fat in response to energy requirements. The liver can also synthesize lipoproteins, cholesterol, and other phospholipids [1; 2].

Protein Metabolism

Before amino acids can be converted into carbohydrates or fat or used to supply caloric needs, a process known as deamination (liberation of ammonia) must occur. The liver is the principal site of deamination and the only site where ammonia is detoxified by conversion into urea. In addition, nearly all the plasma proteins are synthesized in the liver, as are several nonessential amino acids. Serum protein determination measures the liver's ability to maintain a normal level of serum albumin [1; 2].

Storage Functions

Vitamin Storage

The liver is capable of storing up to a four-month supply of vitamins B_{12} and D and up to a 10-year supply of vitamin A for release as needed. Because of this storage capacity, excessive ingestion of vitamin A can have toxic effects on liver function [3; 4].

Iron Storage

Except for the iron stored in hemoglobin, most of the body's iron is stored in the liver as ferritin. Stored iron is released when blood levels of iron fall, a process known as iron buffering [3; 4].

Synthesis of Coagulation Factors

Prothrombin and factors VIII, IX, and X, necessary for effective blood coagulation, are synthesized in the liver. Vitamin K is necessary to promote synthesis for these clotting factors, but if bile secretion is inadequate, absorption of this fat-soluble vitamin cannot occur. The liver also synthesizes fibrinogen, another clotting factor [3; 4].

Detoxification

Many chemicals are detoxified in the liver, including such medications as barbiturates, antidiuretic hormone (ADH), amphetamines, aldosterone, and estrogen. If these substances were not detoxified, they could be fatally toxic to body tissues or organs, or could have other adverse effects (e.g., feminization of men or masculinization of women) [4; 5].

STRUCTURE OF THE GALLBLADDER

The gallbladder is a pear-shaped, hollow, saclike organ about 7–10 cm long that lies in a fossa on the inferior surface of the liver. The cystic duct, which drains the gallbladder, joins with the hepatic duct of the liver to form the common bile duct. Pancreatic secretions also enter this duct via the pancreatic duct. Bile in the common duct enters the duodenum through the sphincter of Oddi. When the sphincter is relaxed, bile can enter the duodenum; when the sphincter is contracted, bile manufactured by the liver is stored in the gallbladder [6].

FUNCTIONS OF THE GALLBLADDER

What are the major regulatory processes of the biliary system?

The major regulatory processes of the biliary system involve the concentration and storage of bile and the regulation of bile secretion [4; 5].

Concentration and Storage of Bile

The hepatic cells can produce from 600–1,000 mL of bile in 24 hours, more than 10 times the 50–75 mL storage capacity of the gallbladder. The mucosa of the gallbladder concentrates bile by absorbing water and electrolytes. This leaves a solution of bile salts, cholesterol, lecithin, and bilirubin that is 5 to 10 times as concentrated as bile secreted by the liver [4; 5].

Regulation of Bile Secretion

When ingested fat enters the small intestine, a hormone called cholecystokinin is released from the intestinal mucosa. Cholecystokinin travels to the gallbladder via the bloodstream, initiating contraction of the smooth muscle in the wall of the gallbladder and relaxation of the sphincter of Oddi. Vagal stimulation also contributes to contraction of the gallbladder. While the hormone secretin, produced by the jejunal and duodenal mucosa, weakly stimulates bile secretion by the liver, peristalsis stimulated by food further relaxes the sphincter of Oddi. These factors combine to produce the sending of bile into the duodenum with each gallbladder contraction and peristaltic wave. The gallbladder empties poorly in the absence of ingested fat but empties completely within an hour if fat is present. Approximately 94% of the bile salts released into the duodenum are reabsorbed and returned to the liver via the bloodstream [5; 6].

PATHOPHYSIOLOGIC INFLUENCES AND EFFECTS

ENLARGEMENT OF THE LIVER

Under normal circumstances, the liver is capable of regeneration following alleviation of an acute condition (e.g., drug toxicity, abscess, inflammation). If the pathogenic influence persists, however, regeneration will be of fibrotic origin [7].

When dead or diseased cells are replaced by fibrous tissue, the liver becomes enlarged (hepatomegaly). Fibrotic scar tissue may impede emptying of blood from the hepatic veins, causing the liver lobules to become engorged. This engorgement leads to further enlargement. Pressure exerted on abdominal nerves by the enlarged liver or displacement of other abdominal organs may cause discomfort or pain. Hepatomegaly may also be related to invasion and multiplication of neoplastic cells [7].

ATROPHY OF THE LIVER

Although the liver may be enlarged during the early stages of hepatic pathology, it eventually atrophies if the pathogenic influence is not removed. In patients with alcohol use disorder, for example, continued ingestion of alcohol combined with malnutrition causes scar tissue to replace the dead cells. In time, the scar tissue shrinks, and the liver becomes smaller than normal. Adjacent organs tend to encroach on the space formerly occupied by the liver. For this reason, a liver from a donor smaller than the recipient is best for transplant purposes [7; 8].

PORTAL HYPERTENSION

Portal hypertension contributes to the development of what serious complication?

As hepatic tissue becomes increasingly fibrotic, the portal veins become compressed. This compression increases back-pressure as portal venous blood volume rises. Portal hypertension results, with pressures in the portal vein as high as 20 mm Hg. This contributes to the development of ascites, the accumulation of protein-rich serum in the peritoneal cavity [7; 8].

Collateral pathways develop between the portal and systemic circulation in areas where tributaries of portal and systemic veins are in close approximation. As portal pressure increases, all collateral pathways between the portal and systemic circulation enlarge [8].

Collateral vessels in the lower esophagus dilate because they are not anatomically structured to carry the extra blood shunted via the azygous system. These dilated veins, called esophageal varices, may rupture, causing massive hemorrhage. Hemorrhoids (rectal varices) can result from the increased pressure in hemorrhoid veins. Splenomegaly can develop secondary to engorgement of the splenic veins [8].

When esophageal varices hemorrhage, treatment is complicated by abnormalities in blood coagulation related to impaired hepatic function. As bile production becomes impaired, absorption of vitamin K is also impaired. Insufficiency or lack of vitamin K leads to decreased production of prothrombin and coagulation factors VIII, IX, and X. Insufficient clotting factors, in turn, is related to increased clotting times. This pathogenic sequence may be signaled by ecchymosis all over the body, bleeding of the gums, or blood in the stool [8].

IMPAIRMENT OF GAS EXCHANGE

Although the vascular dehydration seen in hepatic failure may mask erythrocytopenia, red blood cell deficiency does occur in relation to several factors. For example, the impaired liver cannot store sufficient B_{12} and iron for erythrocyte synthesis. In alcohol-related pathologic states, ingestion of large quantities of alcohol inhibits renal synthesis of erythropoietin; the blood contains a higher proportion of immature erythrocytes and fewer mature red cells. This deficit may manifest as dyspnea, increased cardiac output, cardiomegaly, and clubbing of the fingers [7; 8].

INCREASED SUSCEPTIBILITY TO INFECTION

Injury to the liver is accompanied by damage to or destruction of the Kupffer cells. Phagocytosis is impaired. Micro-organisms enter the general circulation and may form abscesses in the liver tissue itself. Whereas the normal liver accounts of 25% of the body's production of lymphocytes, the diseased liver is incapable of lymphocyte production. Lymphocytopenia increases the body's susceptibility to infection [7; 8].

IMPAIRMENT OF BILIRUBIN EXCRETION

In a compromised liver, absorption and conjugation of bilirubin are impaired. Increased levels of unconjugated bilirubin in the blood and body fluids leads to jaundice, or icterus. The skin becomes yellowish and pruritic, renal excretion of unconjugated bilirubin causes the urine to become mahogany colored, and the stools are clay colored (acholic) due to the absence of stercobilin [7; 8].

Not all cases of jaundice are related to impairment of bilirubin conjugation. For example, if the common bile duct is obstructed by gallstone (choledocholithiasis) or a neoplasm, bilirubin that has been conjugated by the liver cannot be excreted into the duodenum. Levels of bilirubin rise, and the symptoms of jaundice occur. Jaundice may also be related to cholecystitis (inflammation of the gallbladders) or to spasms of the sphincter of Oddi, often associated with cholelithiasis [8].

Inability of the liver to remove the overproduction of bilirubin related to hemolytic states is another cause of jaundice. For example, reaction to a blood transfusion can induce a hemolytic state. The production of unconjugated bilirubin exceeds the conjugation capacity of the liver and levels of circulating unconjugated bilirubin rise. In newborn infants, a deficiency of glucuronyl transferase, the enzyme necessary for bilirubin conjugation, may lead to development of jaundice. This type of jaundice may usually be corrected by exposing the infant to ultraviolet light therapy [8].

Some hereditary disorders sere also associated with jaundice, including Gilbert syndrome and Dubin-Johnson syndrome. Gilbert syndrome is associated with deficiency of glucuronyl transferase, while Dubin-Johnson syndrome is associated with impaired hepatic excretion of bilirubin [8].

BILIARY INFECTIONS

In the presence of inflammation or obstruction, the gallbladder may become swollen by accumulated mucus secretions or purulent drainage. Staphylococcal, streptococcal, or enteric organisms may infect the gallbladder, or it may become gangrenous [9].

AMMONIA TOXICITY

As the functional capacity of the liver diminishes, the ability to convert ammonia to urea for excretion by the kidney is impaired. Moreover, the collateral circulation caused by portal hypertension allows ammonia formed in the intestines to bypass the liver and enter the general circulation. The combined effect of these phenomena is ammonia toxicity. This toxicity manifests itself in hepatic encephalopathy, an altered mental state that begins with confusion and progresses to combative states and ultimately to hepatic coma. Another characteristic symptom of ammonia toxicity is asterixis, a flapping tremor of the hands [9].

ALTERNATION IN NUTRITION-RELATED FUNCTIONS

Injury to hepatic cells compromises bile production and interferes with other nutrition-related hepatic functions, such as synthesis of glycogen. The decrease in appetite that often occurs in liver disease is followed by weight loss, subnormal body temperature, fatigue, and the metabolism of body fat and muscle to meet caloric requirements. Impairment of bile secretion leads to fat intolerance and deceased fat absorption. The use of muscle mass as an energy source combined with decreased capacity for urea formation leads to a negative nitrogen balance. The limbs become emaciated while the abdomen swells with ascites. Skin breakdown is common. Inability to metabolize the amino acid methionine adequately produces fetor hepaticus, a sweet breath odor resembling acetone or old wine [9; 10].

Deficiencies of folic acid and the B complex vitamins often occur in patients with alcoholic liver disease. Alcohol increases the demand for B vitamins, impairs absorption of folate and the B vitamins, and generally contributes to an inadequate consumption of all nutrients. Folic acid deficiency is manifested by a macrocytic anemia, glossitis, and diarrhea. Lesions of the oral mucosa and tongue, fissures at the corners of the mouth (cheilosis), and peripheral neuropathies result from lack of B complex vitamins. Patients with bleeding tendencies require additional vitamin K [9; 10].

Diminished fat absorption leads to deficiencies of the fat-soluble vitamins A, D, E, and K. Night blindness is associated with deficiency of vitamin A. Osteoporosis may occur in relation to vitamin D deficiency, putting the patient at risk for fractures. Vitamin E deficiency can cause impaired red blood cell survival in adults [9; 10].

ALTERATIONS IN FLUID VOLUME

Among the substances synthesized by the normal liver is the plasma protein albumin, which is necessary for maintaining the colloidal osmotic pressure of the plasma. If plasma albumin is insufficient or absent the normal colloidal osmotic pressure of the blood is not maintained. Plasma seeps into the interstitial spaces, causing peripheral and dependent edema. Pulmonary edema may lead to right-sided congestive heart failure. Ascites may be related to hypoalbuminemia and failure of the liver to detoxify aldosterone, as well as to portal hypertension. Accumulations exceeding 2 L may lead to difficulty breathing from pressure on the diaphragm, decrease in appetite, increased feeling of fullness, constipation, flatulence, and umbilical hernia. The weight and bulk of the fluid may also restrict activity [9; 10].

IMPAIRMENT OF DETOXIFICATION

The diminished detoxification capacity of the compromised liver may compound problems related to hypoalbuminemia. Increased levels of circulating aldosterone and ADH increase retention of sodium and water, respectively, further complicating the patient's edema. Intravascular dehydration (lack of plasma in the blood vessels) related to hypoalbuminuria, may mask erythrocytopenia, because the dilution state of the blood has been altered [10; 11].

Alteration in detoxification may also induce other problems related to excessive levels of hormones, chemicals, or drugs. Changes associated with an excess of estrogen may occur, including loss of axillary, pubic, and body hair; soft skin; and gynecomastia and testicular atrophy in men. Decreased libido, impotence, spider angiomas, and palmar erythema are also associated with increased estrogen levels. Alcohol, antibiotics, psychotropic drugs, and some antihypertensive medications may also accumulate in toxic levels when liver function is impaired [10; 11].

RELATED SYSTEMS INFLUENCES AND EFFECTS

Because the hepatobiliary system performs multiple functions related to several other body systems, impairment of hepatobiliary function can affect these systems to varying degrees.

INTEGUMENTARY SYSTEM

Where are xanthomas and xanthelasmas most commonly seen?

Yellowing of the skin is characteristic of jaundice. Pruritus (itching) associated with jaundice may become so severe that patients scratch until they bleed. The break in skin integrity increases the patient's susceptibility to infection [11].

Xanthomas and xanthelasmas may occur in patients with biliary problems in whom serum cholesterol levels are high. These foamy, cholesterol-filled cells may appear anywhere on the body but are commonly seen on the hands and around the eyes [11].

Edema and poor nutritional status also may make the skin susceptible to breakdown. Pressure injuries may form within hours in patients who are not frequently repositioned. White nails, in which 80% of the proximal nail bed is white leaving a distal band of normal pink, are often associated with cirrhosis. In hepatolenticular degeneration (Wilson disease), the lunulae (half-moons in nail beds) are colored light blue instead of the normal white [11].

CARDIOVASCULAR SYSTEM

Fluid overload or congestive heart failure may occur in response to excessive levels of aldosterone and ADH. Reduced oxygen-carrying capacity from erythrocytopenia may lead to increased cardiac output, as the heart labors to deliver oxygen to starved tissues. Increased portal vein pressure related to hepatic fibrosis increases pressure within adjacent vessels and thereby leads to esophageal varices, splenomegaly, and periumbilical dilatation. Hemorrhage of esophageal varices may further reduce the erythrocyte count. Increased clotting time because of efficiency in coagulation factors may produce hemorrhage and hypovolemic shock [11].

NEUROLOGIC SYSTEM

Ammonia toxicity is related to alteration in mental states ranging from confusion to hepatic coma. A patient who is confused or combative has a high potential for injury [11].

PSYCHOSOCIAL/LIFESTYLE INFLUENCES AND EFFECTS

Like all body systems, the hepatobiliary system both influences and is influenced by psychosocial factors.

SEX AND AGE

What groups are at increased risk for contracting viral hepatitis?

Cholelithiasis (gallstones) occurs in women four to five times as often as it does in men. This increased incidence is thought to be related to the action of estrogen and progesterone, which increase the cholesterol saturation of bile. The higher the cholesterol saturation, the greater the risk that gallstones will form. Pregnant women and those taking oral contraceptives are at even higher risk of developing cholelithiasis, especially those who have had several pregnancies or who have been on oral contraceptives for several years [12].

Cholelithiasis is more common in individuals older than 40 years of age; however, it can occur at any age, especially in association with risk factors such as high fat intake, obesity, diabetes, multiple pregnancies, or oral contraceptive use [12].

Young adults and older individuals are at greater risk of contracting viral hepatitis. This increased risk may be associated with poor nutrition or with crowded or unsanitary living conditions [13].

Older adult persons are susceptible to problems of drug toxicity, in part because renal and hepatic function declines with age. At 70 years of age, renal and hepatic efficiency may be half what it was at 20 years of age, yet the prescription of medications for elderly patients often do not reflect this fact. If dosage adjustments are not made, a drug may be prescribed at twice the dosage actually needed. If the patient misunderstands dosage instructions or increases the dosage in the supposition that "more is better," toxic reactions can occur. Older adults often have multiple health problems, and several different healthcare providers may inadvertently prescribe medications that interact unfavorably. Self-medication with over-the-counter remedies (especially laxatives) may compound the overdosage [14].

ALCOHOL AND DRUG ABUSE

Abuse of alcohol is a factor in many, though by no means all, conditions that damage the liver. In addition, drug abuse, especially of injected substances, is associated with an increased risk of contracting hepatitis [15].

LACK OF SANITATION

Drinking water or water used in preparation of foods (e.g., washing fresh fruit or salad greens) may become contaminated by secretions or fecal material from persons with viral hepatitis (A or B). Shellfish caught in waters contaminated by untreated or inadequately treated sewage may also transmit hepatitis A virus. As such, sanitation is an important factor in the control of hepatitis. Nurses, especially those working in community settings, can help inform their patients of the importance of washing hands before handling food and after using toilet facilities [15; 16].

DIETARY HABITS

High-fat diets can contribute to the development of cirrhosis of the liver as well as to gallbladder disease, and biliary diseases are more common in cultures in which food is prepared mostly by frying or large amounts of fat are used in cooking. Conversely, the incidence of gallbladder disease is low in African and South American countries in which fat consumption is low. Due in part to the popularity of fast-food chains and fried snack products, the typical American diet is high in fat. A high intake of alcohol and associated malnutrition also contribute to the development of hepatic and biliary disease [17].

ECONOMIC FACTORS

Although malnutrition is usually associated with poverty, a high income does not ensure a balanced diet. Reliance on fast foods and snack foods and consumption of a fat-laden diet occur in all socioeconomic classes. Poor sanitation and high alcohol consumption may also occur at any income level [17].

OCCUPATION AND AVOCATION

Exposure to all types of hepatitis is a special risk for healthcare professionals, who may be exposed to virus-contaminated blood or secretions. Laboratory and operating room personnel and those who work in hemodialysis units are at particular risk of contact through exposure to body fluids. Nurses administering intravenous therapy or disposing of secretions may be exposed to hepatitis if strict asepsis and isolation principles are not followed. In addition, dentists may be exposed to the hepatitis virus in the saliva of a hepatitis carrier or a person with active disease [18].

Exposure to toxic chemicals may be related to occupation, leisure-time hobbies, or a pharmaceutical regimen. Halothane and chloroform, to which operating room personnel are exposed, are hepatotoxic. Carbon tetrachloride, used in dry cleaning and in various industrial processes, is hepatotoxic, as are toluene and other chemicals used in paint thinners and other compounds used by both professionals and hobbyists. Gold, used in the jewelry trade and in the fabrication of some electronic components, is also hepatotoxic. Among the medications that may have a toxic effect on the liver are a number of antibiotics (including erythromycin, oxacillin, and clindamycin), some psychotropic medications, and oral contraceptives. Highly stressful occupations or those that require a great deal of socialization may contribute to alcohol use disorder.

In taking the health history, nurses should be alert to these psychosocial factors that can help identify patients who appear to be at risk and refer them for detection of early pathological conditions affecting the hepatobiliary system [18].

NURSING ASSESSMENT: ESTABLISHING THE DATA BASE

SUBJECTIVE DATA

In assessing a patient's health status, the health history furnishes valuable clues to past and present problems, as well as to risk factors that can help predict the risk for future problems. Usually, the patient is the chief source of information, but family members also may be able to contribute useful data [19; 20; 21].

The patient should be questioned about any recent loss of weight, change in appetite, or changes in bowel patterns. What color are the patient's stools? What color is the urine? Clay-colored stools or mahogany-colored urine suggests obstruction of the common, hepatic, or cystic ducts or an abnormality of bilirubin excretion. Is a change in color of stool or urine accompanied by yellowing of the sclera or the skin? Did pruritus occur when these changes were noticed? Associating these symptoms may help the patient recall when they began [19; 20; 21].

Has the patient lost weight or lost interest in food? A positive reply might suggest the development of hepatitis or hepatic cancer, depending on other symptoms and signs elicited during the assessment. What does the patient usually eat? High fat intake might suggest cholelithiasis. Does the patient bruise easily or bleed for a long time after a minor cut? Decreased absorption of vitamin K may be associated with hyperbilirubinemia, which can affect blood coagulation and the clotting cascade [20; 21; 22].

Edema of the ankles, difficulty breathing, and collection of fluid in the abdomen could indicate right-sided heart failure, hypoalbuminemia, portal hypertension, or inadequate detoxification of ADH and aldosterone. The patient may not remember when such changes began, but asking when clothing became tight around the waist or shoes no longer fit can help to pinpoint onset [20].

Has the patient had frequent infections? Increased incidence of infection may be related to destruction of Kupffer cells. Has the patient been exposed to hepatitis or mononucleosis? Has the patient had any recent blood transfusion? A positive answer may be correlated with the evidence suggesting hepatitis. Impotence or loss of libido may be related to impaired estrogen detoxification. Determining whether alcohol use might be related to liver dysfunction also requires discretion and tact. One should not presuppose that the patient has alcohol use disorder, even if the suspected disorder is commonly associated with consumption of alcohol. The patient who does have an alcohol problem may be reluctant to answer, may evade questions, or may deny any drinking problems. In some cases, family members will verify unexplained changes in behavior that may suggest alcohol use disorder [20].

Specific, nonjudgmental questions are most likely to yield useful data about drinking habits. Possible questions include:

- What do you like to drink?
- How often do you drink? Every day? Several times each day? Week? Month? Such specifics are more useful than generalities such as "rarely" or "often."
- How much do you drink? One drink? Three or four?
- Does wine with dinner mean a glass or a carafe? By "a few beers" do you mean couple of cans? A six pack?
- When you drink, how much do you consume in 24 hours?
- What is the most you've drunk in 24 hours?
- Do you drink in the morning? At or after work? With friends? Alone?

- Have you ever blacked out?
- Does drinking make you sick or does it make you feel better?

Remember that alcohol in any form (wine, beer, or hard liquor) has the same effect. A 12-oz. bottle of beer, a 4-oz. glass of wine, and a 1-oz. shot of Scotch contain the same amount of alcohol. It is also important not to concentrate on alcohol while ignoring other clues. What is the patient's occupation? Does it involve exposure to solvents, dry-cleaning solutions, anesthetic agents, or other hepatotoxic substances? Does the patient have hobbies that might have hepatotoxic side effects (e.g., furniture refinishing) [20]?

OBJECTIVE DATA

Physical Assessment

What physical findings are suggestive of cirrhosis?

Physical assessment of the patient with hepatobiliary dysfunction involves careful inspection of the skin, nails, and hair. Physical findings that suggest cirrhosis include:

- Ascites
- Ankle edema
- Muscle wasting
- Dilated periumbilical veins (caput medusa)
- Ecchymosis
- Spider angiomas
- Loss of body hair
- Gynecomastia (breast enlargement in males)
- Jaundice (yellow coloration to skin and sclera)
- Clubbing of the fingers

If the patient is in a late stage of liver dysfunction, asterixis related to ammonia toxicity and impending coma will be observed; in these patients, the hands rapidly clench and unclench. Inflating a blood pressure cuff on the arm will worsen the tremor. Asterixis may also be seen in patients with cancer of the liver. In patients with hepatitis, however, only ecchymosis and jaundice will be apparent, unless the condition is long standing. Bruising and jaundice may sometimes accompany hepatic abscess; however, diminished appetite is often the only sign of this disorder. As mentioned previously, jaundice may also be secondary to an obstructive condition or an abnormality affecting bilirubin conjugation [20].

The abdomen should be auscultated before it is palpated. Diminished bowel sounds are common in patients with ascites. At the same time, auscultation of the lungs may elicit evidence of rales or rhonchi related to pulmonary edema. Listen for hepatic bruits, which may be heard with hepatic carcinoma [20].

Hepatomegaly and splenomegaly can be present in patients with hepatitis, cholecystitis, hepatic abscess, mononucleosis, cirrhosis, or liver cancer. Because of the danger of damaging or rupturing these organs, the one should generally avoid palpating the liver or spleen unless they are experienced in this type of examination. If enlargement is severe, these organs may be felt by very light palpation of the abdomen. Swollen lymph nodes may be palpable in the neck or in the groin with an infectious disorder such as mononucleosis [20].

If possible, percussion for measurement of liver size and the usual area of splenic dullness helps determine whether either organ is enlarged. The normal liver span at the midclavicular line (MCL) is 6–12 cm. When percussing liver size, begin low in the abdomen, below the umbilicus, and percuss up the right MCL. The percussion note heard initially is tympany, reflecting air in the bowel. The lower border of the liver is identified when the percussion note changes to dullness. To identify the upper liver border, begin above the nipple, percussing downward along the right MCL. When the percussion note changes from resonance to dullness, the upper liver border has been located. Measure the distance between these two points to determine liver size. Abnormal findings include feeling the liver more than 1 cm below the costal margin [20].

The normal adult spleen lies behind the ninth and eleventh ribs, at or slightly posterior to the left midaxillary line (MAL). The spleen can be located by percussing downward in the intercostal space (ICS) at the left MAL, beginning in the eighth left ICS. The percussion note should change from resonance to splenic dullness at about the tenth left ICS. A large area of dullness may indicate feces in the splenic flexure of the colon, a full stomach, or splenomegaly. Note that patients who have had organ transplants may have undergone splenectomy [20].

Three assessment techniques can be used to determine whether fluid is present in the abdomen:

- With the patient supine, both flanks may be percussed for dullness, which indicates the presence of fluid.
- When the patient assumes a side-laying position, fluid will fall toward the sides on which the patient is lying, where it may be percussed for dullness.
- The presence of a fluid wave may be determined by having the patient lie flat and place his or her hand, ulnar side down, along the abdominal midline and apply pressure to anchor the fat in the mesentery. (If the patient is too ill to participate, an assistant can do this.) Place one hand on one flank to detect signs of a fluid wave while tapping the opposite flank with the other hand. There will be a short time lag between the tap and receipt of the impulse.

Abdominal girth should be measured daily. Measurements taken at the same location (at the level of the umbilicus) assist in evaluating progression and/or treatment of ascites [20].

DIAGNOSTIC STUDIES

Hematologic Studies

Blood samples for determination of white blood cell count (WBC), prothrombin time (PT), hemoglobin level (Hb), and hematocrit (Hct) may be drawn at any time. Hemoglobin and hematocrit values are unaffected by early stages of hepatic disease but may drop if there is hemorrhage from esophageal varices and in response to malnourishment. Prothrombin time will increase with vitamin K deficiency, as may occur with cirrhosis, hepatitis, cholecystitis, cholelithiasis, mononucleosis, or liver cancer. Leukocyte levels increase in patients with mononucleosis, hepatitis, and abscesses [23; 24; 25].

Serum Enzyme Studies

What specific values are likely to be elevated with liver or gallbladder disease?

Elevated serum enzyme levels occur when hepatic cells are damaged and enzymes are released into the blood. Specific values that are likely to be elevated with liver or gallbladder disease include:

- Lactic dehydrogenase (LDH)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Gamma-glutamyl transpeptidase (GGT)

LDH, AST, and ALT values are significantly increased in obstructive jaundice and mononucleosis; they are also markedly elevated in acute and toxic hepatitis, cirrhosis, and hepatic neoplasia. Alkaline phosphatase levels, important in measuring biliary obstruction, are extremely elevated in obstructive jaundice, significantly elevated in liver cancer and mononucleosis, and slightly elevated in hepatitis (viral or toxic) and cirrhosis. Elevation of GGT is the most accurate enzymatic indicator of hepatic disease. Enzyme levels will rise as the disease progresses, peaking at the time of maximum cell death, and then begin to fall [23; 24].

Serum Lipid Values

Changes in serum lipid values are related to the type of disorder. Serum lipids are elevated in obstructive disorders of the biliary system, such as cholelithiasis or neoplasia. They are decreased in disorders causing the destruction of hepatic cells (e.g., cirrhosis, hepatitis) [23; 24].

Bilirubin Values

Studies of bilirubin values are important in determining the cause of jaundice and hyperbilirubinemia. Direct or conjugated bilirubin levels will be elevated if biliary ducts are obstructed and conjugated bilirubin cannot be excreted. Indirect or unconjugated bilirubin levels will be high if parenchymal (liver lobule) cells have been damaged [23; 24].

Elevated levels of urobilinogen in the urine indicate parenchymal liver disease, such as cirrhosis, toxic or infectious hepatitis, or infectious mononucleosis, or they may indicate cholelithiasis. By impairing the excretion of bilirubin in the stool, these conditions lead to increased excretion by the kidneys. Urine that contains bilirubin develops a yellow foam when shaken. Fecal levels of urobilinogen are decreased if the bile ducts are obstructed, but this test is rarely performed because of the difficulty in obtaining accurate values. A 24-hour urine collection would be done to determine the presence and level of urobilinogen [23; 24].

Blood Ammonia Values

Blood ammonia values rise when cirrhosis is present, because the disease impairs the conversion of ammonia to urea for renal excretion. Bleeding esophageal varices exacerbate ammonia toxicity, because the ammonia produced by the action of intestinal bacteria on the protein in blood adds rapidly to already elevated serum ammonia levels. Hepatic coma can result [23; 24].

Other Laboratory Test Values

Changes in serum protein levels are common in hepatic and biliary disorders. Serum albumin levels drop (hypoalbuminemia) and gamma globulin levels rise when parenchymal cell damage occurs. Serum antigen-antibody levels help identify and type hepatitis. For example, hepatitis B surface antigen (HBsAg) is present in the blood of persons who have hepatitis B and also in those who are carriers of the disease. Patients with hepatitis B surface antibodies (anti-HBs) in their blood have immunity to hepatitis B [23; 24].

Ultrasound

For some patients, especially those for whom oral cholecystography or cholangiography are contraindicated, ultrasound offers a noninvasive alternative. This technique is being used with increasing frequency to investigate ambiguous findings obtained by other techniques. It is useful in differentiating benign cysts and tumors from malignancies. Liver abscesses and dilation of intrahepatic ducts can be identified by ultrasound, as can gallstones, biliary tumors, and tumors of the extrahepatic ducts. In a patient with jaundice, dilation of the extrahepatic ducts suggests extrahepatic obstruction. If the ducts appear normal, jaundice is likely to be related to extrahepatic or prehepatic conditions. Hepatic icterus is related to abnormalities of bilirubin conjugation or excretion. Extrahepatic icterus is related to obstruction of the hepatic, common, or cystic bile ducts. Prehepatic icterus is associated with an abnormality that takes effect before circulating bilirubin reaches the liver (e.g., hemolysis of neonatal icterus) [23].

Nursing Implications

To ensure that the gallbladder is a maximum size for the test, the patient must be kept NPO after midnight on the day of testing. Were the patient to eat, contraction and emptying of the gallbladder would reduce its size, making it more difficult to visualize. NPO orders are not necessary for visualization of the liver. If barium contrast studies have been performed prior to the ultrasonography, a laxative will be ordered to cleanse the bowel of residual contrast medium [23].

In explaining the procedure to the patient, the nurse can offer reassurance that the study is not painful. The patient should be prepared for the copious amount of lubricant that will be applied to the skin to enhance the transmission of the sound waves. The rationale for any NPO order should be explained. The procedure will take about 20 minutes [26; 27].

Liver Scan

For the liver scan, a radionuclide is administered intravenously. Thirty minutes later, a detecting device is passed over the patient's abdomen to record the distribution of radioactive particles in the liver. Although this technique exposes the patient to far less radiation than x-rays, it can only demonstrate filling defects greater than 2 cm in diameter. It is contraindicated for pregnant patients and those who might have difficulty lying still during the scan, which takes about one hour [23; 28; 29].

No special preparation is required for this study. The procedure should be fully explained to the patient, including that small amounts of radioactive substances are used. Some patients may be apprehensive about the amount of time required for the scan, and it is helpful to explain that the scanning device does not emit radiation but rather records radiation emanating from the injected radioisotope. Pregnant healthcare providers should not be assigned to the patient for at least 24 hours after the radionuclide injection [26; 27; 28].

Dye Clearance Studies

For dye clearance studies, the patient fasts for 12 hours prior to the test. Dye is injected intravenously (about 5 mg/kg of body weight). Blood is drawn 45 minutes after the injection and inspected for the presence of dye. Normally, less than 5% of the dye will be found in the serum; the presence of a greater proportion of the dye indicates liver cell damage, as the impaired cells cannot absorb the dye from the blood. If hepatic damage is known to exist, lower dosages of dye are administered. The indocyanine green (ICG) clearance test is the most widely used quantitative liver function test [23; 28; 30].

Oral Cholecystography

An oral cholecystography, or gallbladder series, provides visualization of the gallbladder following oral ingestion of a radiopaque iodinated dye. In the first test of the series, gallstones (when present) may be visualized as dark shadows in a dye-filled gallbladder. Satisfactory visualization of the gallbladder can be obtained only if the gallbladder has concentrated the dye. Adequate concentrating depends on correct dosage of the dye, adequate absorption of the dye from the gastrointestinal tract (no nausea or vomiting), and absence of food in the digestive tract (NPO after midnight). If nonvisualization occurs, the test is repeated the next day with a doubled dosage of dye. Hepatocellular dysfunction, cystic duct obstruction, or inflammation of the biliary mucosa will prevent visualization. The patient's allergy history should be determined prior to testing [23; 28].

In the second phase of the series, the patient is given a fatty meal immediately following the first phase, and x-rays are taken to determine how well the gallbladder empties. The x-rays are repeated every 30 minutes until the dye is gone and the gallbladder can no longer be visualized. This may take one to five hours, but usually takes no more than three [23].

This is an older study that is rarely used today, as ultrasound or computed tomography (CT) are more accurate, faster techniques for identifying gallstones without exposure to iodine. Ultrasonography is typically the preferred modality, because it is less invasive, more accurate cholelithiasis, and can be safely used with most patients. In general, use of oral cholecystography is limited to cases in which gallstones are strongly suspected but ultrasonography does not show them. If it is indicated, oral cholecystography is contraindicated for pregnant women, patients too ill to swallow the tablets or to eat a meal, and persons allergic to iodine [23].

Patients undergoing oral cholecystography are required to swallow seven or eight tablets of absorbable iodine dye the evening prior to the test. After the tablets are swallowed, only water may be given until midnight; after midnight, patients are kept NPO. Nursing implications include [26; 27]:

- Verifying that no iodine allergy exists. The patient should be questioned about seafood allergies, as not all patients are aware that these foods contain iodine.
- Ascertaining that the patient is given a low-fat meal on the evening before the test.
- Verifying that serum bilirubin is less than 1.8 mg/dL (so visualization will be possible).
- Explaining the procedure to the patient.
- Administering the tablets at five-minute intervals.
- Observing for adverse effects of the dye (because anaphylactic reactions have occurred).
- Maintaining NPO status.

Oral and Intravenous Cholangiography

Oral and intravenous cholangiography allowed for visualization of the hepatic and common bile ducts in addition to the gallbladder and cystic duct. It was historically used for patients with acute inflammatory disorders, those with proven gallstones, and those who are NPO or unable to tolerate the orally ingested dye used in cholecystography [23; 26; 27; 28].

However, these studies have become obsolete, having been replaced by more advanced technologies, such as the endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTHC) and magnetic resonance cholangiopancreatography (MRCP) [31].

Intraoperative Cholangiography

Cholangiography may be performed during a surgical procedure to ascertain that all calculi have been removed from the common bile duct, reducing the probability of complications or follow-up surgery. Dye is injected to enhance visualization [23; 28].

T-Tube Cholangiography

A T-Tube cholangiography may be taken 7 to 10 days following a cholangiography. The T-tube is placed during surgery. Later, dye is injected via the T-tube so the common bile duct may be visualized and its patency ascertained [23; 28]. As with other older modalities, this technique has been largely superseded by MRCP and ERCP.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

As noted, ERCP, PTHC, and ultrasound have become the most valuable studies for assessment of the biliary tract [31]. ERCP studies allow visualization of the bile ducts as well as benign masses, cysts, and malignant neoplasms [23; 32; 33].

With ERCP, a type of fibrotic endoscope termed a duodenoscope is inserted into the duodenum via the esophagus. Intravenously administered secretin immobilizes the duodenum, facilitating visualization of the ampulla of Vater. Contrast material combined with a broad-spectrum antibiotic are administered through a small cannula inserted into the ampulla, and films are taken periodically for approximately an hour. The antibiotic is given to prevent gram-negative sepsis that may occur if bacteria are forced in the bloodstream by the pressure of the dye injections. Perforation of the esophagus, stomach, or duodenum is another possible complication of ERCP, so this technique is not used for combative patients [23; 32; 33].

A consent form is necessary for this procedure. On teaching the patient about the procedure, explain that an impulse to gag will be felt when the tube is passed. The patient is kept NPO after midnight. Meperidine and atropine are administered intramuscularly before the patient is taken to the radiology department. Emotional support should be given as needed. After the procedure, the patient's pulse, temperature, and blood pressure are monitored for signs of shock that may arise from perforation or hemorrhage and for signs of sepsis. Pancreatitis may occur in response to the pressure exertion on the pancreatic duct during the procedure; therefore, a serum amylase test should be performed on the day following an ERCP [26; 27].

Percutaneous Transhepatic Cholangiography (PTHC)

Like ERCP, PTHC is used for icteric patients with serum bilirubin levels greater than 3.5 mg/dL. During this procedure, a combination of contrast medium and antibiotic is injected into the intrahepatic bile duct to visualize the biliary system. The area below the right costal margin is locally anesthetized, and a spinal needle is inserted directly into the liver, guided by fluoroscopy. When bile appears through the needle, it is withdrawn by syringe. Radiopaque dye is then injected directly into the biliary tree. Fluoroscopy is used to determine filling of the biliary tract [23; 28; 34].

The patient is intravenously sedated during the procedure, which takes about one hour. If obstruction is found, a catheter may be left in place for drainage of bile. A PTHC is contraindicated for patients who have prolonged clotting times or iodine allergy, for patients who have had recent gastrointestinal contrast studies or are unlikely to tolerate surgery, and for combative patients. Bile peritonitis, hemorrhage, and sepsis are possible complications [23].

A consent form is required for this procedure, and coagulation studies as well as information regarding possible iodine allergy must be verified. The patient is kept NPO after midnight. A laxative may be prescribed if gastrointestinal studies using barium have been recently administered. An intravenous infusion is started for venous access, and the patient is premedicated with meperidine and atropine before leaving the unit. After the procedure, the patient is kept NPO. Vital signs should be monitored as for any postsurgical patient. A sterile closed system should be maintained if a catheter has been left in place [26; 27].

Liver Biopsy

The purpose of a liver biopsy is to obtain a sample of tissue for histologic examination. Prior to the procedure, ultrasound may be done to determine the precise location of the liver. A coagulation profile should be obtained so the risk of hemorrhage can be calculated. The patient's blood is typed and crossmatched in case a transfusion is needed. Biopsy is contraindicated if the platelet count is below 100,000/mcL [23; 28; 35].

For percutaneous liver biopsy, the patient is assisted into a supine or left lateral position. The skin is aseptically cleansed and anesthetized, and a small incision is made to allow insertion of a specialized needle into the liver. In the case of transjugular biopsy, the right jugular vein is punctured under ultrasound guidance, and a guide wire is passed through, followed by placement of a 9-French sheath. The wire is then negotiated through the heart at to the right hepatic vein. Placement is verified with hepatic venogram with contrast. A stiffening cannula is placed, then the biopsy needle is introduced. With both techniques, a small core of hepatic tissue is then withdrawn and sent for microscopic evaluation. Following the procedure, the patient should assume the right lateral position to keep pressure on the liver to prevent hemorrhage [23; 28; 35].

These procedures require a consent form. The patient is kept NPO after midnight. Nursing responsibilities include:

- Checking coagulation studies and consent form.
- Maintaining NPO status.
- Recording preprocedure vital signs.
- Providing emotional support for the patient; this procedure can be frightening and uncomfortable.
- Explaining the procedure to the patient, emphasizing the importance of holding still.
- Immediately prior to needle insertion asking the patient to inhale deeply, exhale completely, and hold the breath at the end of expiration. This immobilizes the chest wall and keeps the diaphragm at its upper level during the procedure (which takes 5 to 10 seconds).
- Appling pressure to the biopsy site after needle removal.
- Turning patient onto right side with a pillow under the costal martin to maintain pressure to the site.
- Observing for bile-colored drainage on the patient's dressing. This could indicate that a biliary vessel has been penetrated.
- Monitoring post-procedure vital signs (every 15 minutes for an hour, then every 30 minutes for two hours, then every four hours), and administering comfort measures after the procedure.

The patient should remain immobile on the right side on bedrest for 24 hours and be closely observed for signs of hemorrhage, extravasation of fluid from the biopsy site, peritonitis, and pain. Pain in the right upper quadrant and right shoulder area is common. The patient should be reassured about this while being encouraged to report any change in pain level. Analgesics, if given, must be non-hepatotoxic and must not affect clotting [26; 27].

NURSING DIAGNOSES

Assessment of the patient with hepatic or biliary dysfunction, including evaluation of the patient's health history and results of laboratory tests and diagnostic studies, can lead to many possible nursing diagnoses.

ALTERATIONS IN COMFORT

Pain

Mild or moderate pain may occur in relation to hepatomegaly or splenomegaly associated with hepatitis, hepatic abscess, or infectious mononucleosis. Moderate pain may accompany late cirrhosis and chronic hepatitis. With cancer of the liver, whether the liver is a primary or a metastatic site, pain becomes severe and intractable. Severe, colicky pain in the right upper quadrant is common with cholelithiasis or cholecystitis [36; 37].

Pruritus

Regardless of whether icterus is prehepatic or hepatic, pruritus will be associated with the jaundice. The patient may scratch the skin until it bleeds. The condition may be intensified by damp clothing or bedding caused by perspiration or by poor ventilation [36; 37].

Potential for Impairment of Skin Integrity

If pruritus is severe and the patient scratches frequently, skin integrity may be broken. In cirrhosis and cancer of the liver, edema and negative nitrogen balance cause the skin to be susceptible to breakdown. If the patient does not frequently move, pressure injuries can form within 12 to 24 hours [36; 37].

Sexual Dysfunction and Disturbance in Self-Concept

Disturbance in self-concept may be related to body image alteration and role performance. Softening of the skin, loss of body hair, or gynecomastia may be related to impaired estrogen detoxification. In some, these feminizing changes disturb the patient's sense of masculinity. Ascites and icterus further affect self-image. Complications associated with severe disease such as cancer or cirrhosis (e.g., ascites, pleural effusion) may necessitate the patient changing occupation or retiring. Loss of occupational role can severely damage self-esteem.

Sexual dysfunction may also accompany impairment of estrogen detoxification. Loss of libido may occur in both sexes, and male patients may become impotent. The patient may be hesitant to discuss these matters with healthcare professionals [36; 37].

ALTERATION IN THOUGHT PROCESSES

Ammonia toxicity is related to the inability of the compromised hepatic cells to convert ammonia to urea for excretion in the urine. Ammonia interferes with brain metabolism, leading to alterations of mentation ranging from slight confusion to coma. Initially, patients may be somewhat confused or disoriented—unable, for example, to remember their names or where they are. Asterixis may also be apparent. Patients may then progress through lethargy to combativeness and abusiveness before collapsing into coma. Gastrointestinal hemorrhage further increases serum ammonia levels owing to bacterial action on blood in the gut. Wernicke-Korsakoff syndrome, characterized by confusion, disorientation, and amnesia with confabulation, may develop in patients with alcohol use disorder. The syndrome is related to thiamine deficiency [36; 37].

ALTERATION IN NUTRITION

What vitamin deficiencies are common in patients with hepatic dysfunction?

Hepatic dysfunction is associated with impaired metabolism of proteins, fats, carbohydrates, and vitamins. Weight loss, fatigue, negative nitrogen balance, vitamin B deficiency, and deficiencies of fat-soluble vitamins A, D, E, and K are common.

The patient should be encouraged to consume a balanced diet high in carbohydrates, vitamins, and (unless ammonia toxicity is present) protein. Abdominal pressure from ascites may cause a constant feeling of fullness as well as flatulence and constipation. These conditions may also diminish appetite, further depleting nutritional status. Patients with cirrhosis experience muscle wasting and significant weight loss [36; 37].

In cholelithiasis or cholestasis, a low-fat, low-protein diet should be consumed because fat metabolism is reduced by disturbances in biliary function. Deficiency of vitamin K may also accompany these disorders [17; 21].

IMPAIRMENT OF GAS EXCHANGE

Several conditions related to hepatic and biliary disease impair exchange of oxygen and carbon dioxide. Retention of sodium and water is associated with plural effusion and ascites. Ascites exerts pressure on the diaphragm, interfering with inspiration. Inadequate oxygenation of body tissue related to erythrocytopenia also impairs gas exchange [36; 37].

ALTERATION IN FLUID VOLUME

Alterations in fluid volume may be either deficits or overloads. For example, when the compromised liver can no longer detoxify ADH and aldosterone, retention of sodium and water contributes to circulatory congestion and hypertension. Conversely, fluid volume deficit can be related to hemorrhage of esophageal varices (leading to shock) or to overuse of diuretics. If plasma colloidal osmotic pressure is reduced because of hypoalbuminemia, fluid extravasation into the interstitial space will cause edema despite intravascular dehydration. In this instance, diuretics alone will be ineffective in reducing edema and will, moreover, worsen dehydration [36; 37].

ALTERATION IN TISSUE PERFUSION

Increased cardiac output associated with hypertension is related to fluid volume alteration. Erythrocytopenia can lead to increased cardiac output as the heart attempts to compensate for tissue oxygen needs.

NURSE PLANNING AND IMPLEMENTATION

For the patient with hepatobiliary dysfunction, alterations in comfort are likely to be associated with pain or pruritus.

PAIN RELIEF

What is the first-line treatment for the management of biliary pain?

Mild-to-moderate pain associated with various disorders may be controlled with non-narcotic, non-aspirin analgesics. Patients with hepatic dysfunction are likely to have coagulation abnormalities related to poor absorption of vitamin K. As such, drugs causing hepatic damage should also be avoided; the drugs of choice are those excreted by the kidneys [26].

For pain associated with cholelithiasis, nonsteroidal anti-inflammatory drugs (NSAIDs) provide greater relief of biliary pain and are considered first-line management [38]. NSAIDs have been reported as superior to antispasmodics for pain control. For narcotic management, meperidine is usually the drug of choice; butorphanol or hydromorphone can also be utilized, especially if NSAIDs are contraindicated [39]. Morphine is rarely administered. Nitroglycerin or phenobarbital may promote comfort by relaxing smooth muscle. Nursing measures, such as giving a backrub, assisting the patient in changing position, providing distraction, and offering emotional support, may supplement analgesic medication [27].

PRURITUS RELIEF

Pruritus associated with icterus can be extremely upsetting to the patient. It is important to rule out any possibility that the condition is related to an allergy or irritation. Measures to alleviate itching include dry clothing and bedding, emollients, a well-balanced diet, and distraction. Alkaline soaps should be avoided, and baths should be taken only every two or three days, if possible. Whirlpool baths are preferred [27]. Biliary drainage can help to alleviate related pruritus. If indicated, the preferred pharmacotherapy is with ursodeoxycholic acid; cholestyramine, rifampicin, naltrexone, and sertraline are second-line options.

MAINTAINING AND IMPROVING SKIN INTEGRITY

Several nursing interventions are crucial to the maintenance of skin integrity. Relieving pruritus should be a high priority, and frequent turning and repositioning is necessary to relieve pressure of edematous areas and prevent formation of pressure injuries. A low-sodium diet, fluid restriction, and diuretic therapy may be prescribed to reduce diuresis and lessen peripheral and abdominal edema. It is important to remember that pressure injuries can form in as little as 12 to 24 hours if turning and repositioning are not done conscientiously every 1 or 2 hours [26; 27].

Preventing infection presents a challenge, because the patient's reticuloendothelial system is severely compromised. Careful handwashing is essential. Sterile technique should be maintained during dressing changes for surgical wounds and at catheter sites. Nutritional measures may be used to promote healing and improvement of skin integrity [26].

MAINTAINING AND IMPROVING THOUGHT PROCESSES

Evaluating the patient's mental status, promoting safety, and monitoring for ammonia toxicity are nursing responsibilities. Mentation may be monitored by assessing the patient's orientation to person, place, and time. One convenient technique for detecting changes in ammonia toxicity levels is having the patient write his or her name daily and compare the signatures. Severity of asterixis may be evaluated by pumping up a blood pressure cuff on the patients arm; the more rapidly the hand

clenches and unclenches, the higher the serum level of ammonia. The patient's breath should be assessed for fetor hepatics, which is similar to the odor of acetone or old wine [26; 27].

Nurses should also be alert to the possibility that a hepatotoxic drug or dosage has been inadvertently prescribed. Detoxification capacity declines in older individuals, even under normal conditions; this impairment will be worsened in the presence of hepatic disease [40; 41].

Safety measures (e.g., padded side rails) may be necessary to protect patients who are confused or combative as a result of hepatic encephalopathy. The patient should be reminded not to get out of bed unassisted. Activities of daily living should be supervised [27].

REDUCING AMMONIA LEVELS

Various therapeutic measures may be prescribed to decrease serum ammonia levels. Intravenous administration of glucose may provide protein-conserving carbohydrates. Rest can decrease release of ammonia associated with muscle contraction [27].

Pharmacologic measures may also be employed. Potassium may be given to improve cerebral metabolism of ammonia. Hypokalemia has been identified as being a contributing factor for the increased risk of hepatic encephalopathy. Studies have shown that supplementing and correcting hypokalemia in patients with cirrhosis can decrease ammonia levels [42; 43]. Antibiotics such as neomycin may be administered orally or by enema to reduce the number of ammonia-synthesizing bacteria in the gut. Because neomycin is poorly absorbed from the intestine, its bactericidal action in the intestine is prolonged; however, this antibiotic may cause ototoxicity of nephrotoxicity if administered for more than six days [41; 44]. Metronidazole and rifampin are alternative choices.

Lactulose may be given orally or by nasogastric tube. This acts by acidifying the colon, so ammonia couples with hydrogen ions and is excreted in the feces. Improvement may be seen within 24 hours, with serum ammonia levels being reduced by 25% to 50% in most patients. Diarrhea is common with lactulose therapy, so electrolyte levels should be monitored. In some cases, hemodialysis may be necessary to reduce serum ammonia levels [41; 44].

Nurses should routinely check stools for occult blood and monitor vital signs for changes that might indicate gastrointestinal hemorrhage. If esophageal varices are bleeding, treatments include beta blockers and medical procedures to stop bleeding [27].

IMPROVING NUTRITIONAL INTAKE

Unless ammonia toxicity is present, the patient with hepatic dysfunction should receive a diet high in protein to promote hepatic healing and prevent loss of muscle mass. The diet should be low in salt and high in vitamins, carbohydrates, and calories. If ammonia toxicity is present, potassium-rich foods should be provided. Although limiting protein can help address hyperammonemia, patients with hepatic dysfunction are often malnourished, and limiting protein intake is not generally recommended. Plant protein or milk-based protein can be used in patients with elevated ammonia levels [45]. The patient with biliary dysfunction should reduce the quantity of fats consumed [17].

Promoting a well-balanced diet with a patient who often has no appetite is a challenge. Appetite may be improved by providing oral hygiene and fresh air, minimizing movement, and administering prescribed antiemetics. Consultation with a dietitian is recommended to identify the best approach to feeding, perhaps in small, frequent feedings supplemented by nourishing snacks. As stated, plant protein supplements may be used if not contraindicated. It is helpful if the mealtime environment is pleasant and free of unpleasant odors. Food preferences elicited in the patient history should be considered. Explaining the rationale for the diet may encourage the patient to eat more. If the patient is unable to eat enough to meet caloric needs, feeding via nasogastric tube or total parenteral nutrition may be prescribed [17].

IMPROVING GAS EXCHANGE

Several measures may be prescribed to improve oxygenation. If dyspnea occurs at rest or upon exertion, oxygen therapy may be initiated. Oral iron supplements or a transfusion of packaged red cells may be given to improve hemoglobin and hematocrit levels. Intramuscular injections of vitamin K1 improve clotting. Diuretic therapy or administration of albumin may be prescribed to reduce pleural effusion, which hinders gas exchange, or to decrease ascites, which exerts pressure on the diaphragm [27].

Nurses may be called upon to assist with paracentesis to remove ascitic fluid from the abdomen. The patient is assisted to a sitting position. The abdomen is cleansed with an antiseptic solution and draped. Local anesthesia is administered, and a trocar is inserted and tubing attached. Fluid drains via gravity into a sterile container. Up to 2 L of fluid may be removed; removal of a larger quantity may lead to shock. The amount and color of ascitic fluid removed should be documented before sending a sample for laboratory evaluation. Paracentesis may be repeated periodically as fluid accumulates [27]. Ascites may also be controlled by a LeVeen or Denver shunt procedure, which will be discussed later in this course.

RESTORING NORMAL FLUID VOLUME

Edema related to hepatic dysfunction can be misleading, because vascular dehydration frequently accompanies it and diuretic therapy alone can worsen dehydration. Diuretics should not be overused and should be given in conjunction with albumin. Aldosterone antagonists are the diuretics of choice, as edema is related to inadequate detoxification of aldosterone. Intake-output records should be maintained

and electrolyte values and skin turgor assessed. The patient should be weighed and girth measured daily to assess fluid volume status; weight loss should not exceed one-half pound (0.23 kg) per day. Greater losses may result in a shift of fluids into the abdominal cavity, promote electrolyte imbalance, and precipitate hepatic encephalopathy [27].

In the patient with ascites, accumulated fluid may stretch the skin so tightly that it tears. Patients should be urged to avoid restrictive clothing, take good care of the skin, and change positions frequently. A pillow may be placed under the costal margin for support if the patient is lying on his or her side. Compression stockings may be worn and the limbs elevated frequently to minimize peripheral edema. When seated, patients should be warned to support their legs, not to cross them or let them dangle. A fluid deficit may occur during episodes of variceal hemorrhage. Lost blood should be replaced, and vital signs closely monitored. Fluid restrictions of 1,000 mL in 24 hours may be required when peripheral edema and ascites are present [27].

IMPROVING TISSUE PERFUSION

Tissue perfusion may be improved by correcting anemia; iron supplements, vitamins B12 and K, and blood transfusions may be administered. When hemoglobin and hematocrit values are restored to normal levels, the heart pumps blood throughout the body more efficiently. Ecchymosis and gingival hemorrhage may indicate vitamin K deficiency. If the patient has coagulation disorders, intramuscular injections should be avoided whenever possible and pressure should be applied after any injection is given. Decreasing fluid overload, if present, will improve cardiac output [27].

NURSING EVALUATION

COMFORT

Nursing interventions related to alleviation of pain are considered successful when the patient is resting comfortably without severe pain and can perform activities of daily living (ADLs) without undue discomfort. Observations verifying these outcomes would include sleeping soundly for at least four hours at a time, absence of facial grimaces, and absence of listlessness [36].

Nursing interventions related to pruritus are successful if the patient has relief from itching, rests comfortably without scratching, performs ADLs without scratching, and does not interrupt skin integrity by scratching [36].

SKIN INTEGRITY

Absence of pressure injuries or erythema at surgical and intravenous sites, normal temperature, and evidence that the patient is eating the prescribed diet support an outcome of maintaining or improving skin integrity [37].

THOUGHT PROCESSES

Orientation to person, place, and time, absence of asterixis, and the ability to write one's name the same way on sequential days are evidence that a patient's thought processes are intact. If asterixis develops or changes in handwriting are noted, the nurse may need to modify plans and interventions [37].

NUTRITION

Expected outcomes for improving nutritional status and knowledge of nutrition include the ability to list foods high in protein and potassium and low in salt and fats, evidence of increasing intake of well-balanced foods, and signs that nutritional deficiencies are being corrected. This can be a slow process. Consulting with the patient to make a list of favorite foods and seeing that those foods are served may improve consumption. Cultural and ethnic preferences should be considered in planning the diet [37].

GAS EXCHANGE

One expected outcome might be the patient's ability to ambulate without oxygen supplementation. Another is return of the hemoglobin level to normal. There might be an absence of dyspnea on exertion; an absence of cyanosis; or increased energy (e.g., ability to engage in usual activities). If these data can be observed, the nursing plan may be considered successful [37].

FLUID VOLUME

Expected outcomes related to fluid volume include good skin turgor, decreased circumference of edematous extremities or abdominal girth, and intake and output measurements are indications of correction of a fluid alteration. Correcting fluid volume alterations may take a long time, and several plans and revisions may be required [37].

TISSUE PERFUSION

A blood pressure no greater than 140/80 mm Hg and normal hemoglobin and prothrombin time are indications of adequate tissue perfusion. However, it is important to remember that hemoglobin and hematocrit values and blood pressure readings may be deceiving if vascular dehydration is present [37].

CONGENITAL DISORDERS

Congenital disorders of the hepatic and biliary system are present from birth, although they may not be visibly apparent or symptomatic until adulthood. These patients may seek medical care when symptoms of their disorder first appear or when exacerbations occur [46].

GILBERT SYNDROME

Gilbert syndrome is a familial disorder characterized by a deficiency of glucuronide transferase, an enzyme necessary for conjugation of bilirubin. Due to the enzyme insufficiency,

serum levels of unconjugated bilirubin rise, with consequent hyperbilirubinemia and icterus. No pathologic changes occur in the liver with this disorder, so liver function studies will yield normal results except for the elevated bilirubin levels. There is no hemolysis or obstruction [46; 47]. Differential diagnosis includes non-alcoholic fatty liver disease, autoimmune hepatitis, drug-induced hepatitis, and primary biliary or sclerosing cholangitis.

In general, there is no required treatment for Gilbert syndrome aside from symptom management. Steps should be taken to avoid potential triggers in order to minimize fluctuations in unconjugated bilirubin. If there is evidence of hepatic decompensation, the patient should be referred to a specialist for further evaluation.

ALAGILLE SYNDROME

What are the main clinical manifestations of Alagille syndrome?

Alagille syndrome is a genetic disorder with manifestations in multiple systems throughout the body. Variability in presentation is seen even among individuals from the same family [48]. The major clinical manifestations of this disorder are bile duct paucity on liver biopsy, cholestasis, congenital cardiac defects (primarily involving the pulmonary arteries), butterfly vertebrae, ophthalmologic abnormalities, and characteristic facial features. The diagnosis is made through positive genetic testing and/or clinical diagnostic criteria.

Clinical management of Alagille syndrome is primarily supportive. For some patients, targeted therapy with ileal bile acid transporter inhibitors (e.g., maralixabat and odevixibat) may be indicated to increase the excretion of bile acids. In severe cases, liver transplantation may be indicated. Measures to address pruritus, xanthomas, and pain are recommended. Considering the multisystem manifestations of this syndrome, these patients benefit from care delivered by an interprofessional team, including physicians, nurses, dieticians, genetic counselors, and specialists.

Patients with Alagille syndrome should be monitored to allow for early identification of progression and potentially harmful complications. Liver function should be regularly assessed, and serum alpha-fetoprotein and liver ultrasound may be measured every six months [48].

DISORDERS OF MULTIFACTORIAL ORIGIN

Disorders of multifactorial origin are those for which no single, specific etiologic agent has been identified. For the hepatobiliary system, cirrhosis is the major disease process of multifactorial origin [49].

CIRRHOSIS

What are the two clinical categories of cirrhosis?

Cirrhosis is a chronic process in which the normal configuration of liver lobules is disrupted. Cell death occurs, and regeneration is associated with scarring. Nodular cells formed during regeneration distort the morphology of the liver and obstruct hepatic flow of blood and lymph. Eventually, cirrhosis leads to hepatic failure and portal hypertension [50].

Cirrhosis is the end stage of any chronic liver disease. In developed countries, the most common causes include nonalcoholic fatty liver disease, hepatitis infection, and excessive alcohol intake; in developing counties, hepatitis A and B infections are the most likely causes. There are two clinical categories of cirrhosis: compensated and decompensated. Patients who have compensated cirrhosis can be further categorized as:

- Stage 1: No varices, no ascites
- Stage 2: Varices, no ascites

Likewise, patients with decompensated cirrhosis may be staged as:

- Stage 3: Ascites with or without varices
- Stage 4: Bleeding with or without ascites

The diagnosis of cirrhosis can be made by clinical, laboratory, imaging, or liver stiffness findings. For patients with compensated cirrhosis, noninvasive parameters all may be normal and liver biopsy would be required for diagnosis. Decompensated cirrhosis is more easily diagnosed by laboratory analysis.

These patients are asymptomatic and overall have median survival times of more than 12 years. Presence of varices is the key prognostic factor for compensated patients and indicates higher likelihood of decompensation. The Child-Turcotte-Pugh (CTP) score is used as a prognostic scoring system in cirrhosis based on two clinical and three laboratory parameters:

- Ascites:
  - None: 1 point
  - Diuretic-sensitive or mild/moderate: 2 points
  - Diuretic-refractory or tense: 3 points
- Encephalopathy:
  - None: 1 point
  - Episodic or overt grade 2: 2 points
  - Recurrent/chronic or grade 3–4: 3 points
- Albumin:
  - >3.5 g/dL: 1 point
  - 3.4–2.8 g/dL: 2 points
  - <2.8 g/dL: 3 points
- Bilirubin:
  - <2 mg/dL: 1 point
  - 2–3 mg/dL: 2 points
  - >3 mg/dL: 3 points

- International normalized ratio (INR):
  - <1.7: 1 point
  - 1.7–2.3: 2 points
  - >2.3: 3 points

In the original scoring system, nutritional status (normal, moderately altered, malnourished) was used instead of INR, which reflects the importance of sarcopenia in cirrhosis. Patients who score 5–6 points are mostly those with compensated cirrhosis. A score of 7–9 points indicates decompensated cirrhosis, but decompensation is "early." Those who score 10–15 points have later or "further" decompensated cirrhosis. One-year mortality ranges from 1% for mildest disease to 57% for patients with severe disease.

Clinical Manifestations

Cirrhosis is often (but not invariably) part of a progressive disease that begins with fatty infiltration of the liver (steatosis) that progresses to fibrosis of the liver due to inflammation. If not adequately treated, cirrhosis can progress to hepatic failure. Cirrhosis may be related to nutritional disorders, biliary obstruction, hepatotoxicity, iron storage disorders, and alcohol ingestion. Histologic examination of the liver reveals fatty infiltration, cellular necrosis, and disruption of the lobes. Gross inspection reveals a "hobnail" appearance; the hepatic surface is often stippled and nodular [51].

Portal hypertension results in compensatory development of collateral blood vessels in the esophagus. These vessels, called esophageal varices, dilate as portal hypertension increases. Because such vessels are inadequate to accommodate the increased blood flow, hemorrhage may occur [51].

Patients with cirrhosis often have a characteristic appearance. Anorexia develops early in the course of the disease, resulting in significant weight loss. The skin is typically orange-yellow, the eyes are sunken, and the facial bones are prominent. The limbs are emaciated, but the abdomen is enlarged due to peripheral edema or ascites. Other symptoms include spider angiomas, palmar erythema, and changes in mental status [51].

Therapeutic Measures

Hemorrhage of esophageal varices may be controlled temporarily by administering infusions of vasopressin, somatostatin, octreotide, or terlipressin to promote diffuse arterial vasoconstriction and to lower portal pressure by constricting the splanchnic arterial bed. The infusion may be given systemically or via the superior mesenteric artery and administered for five days, according to current guidelines [52]. This provides only temporary control and is associated with complications, including systemic arterial hypertension and coronary vasoconstriction, possibly leading to myocardial infarction. Whole blood should be available for immediate infusion [52; 53; 54]. If medication administration is unsuccessful, gastric lavage with ice-cold saline, use of the Minnesota tube or Sengstaken-Blakemore tube, or portal-systemic shunting may be implemented to control bleeding temporarily.

As noted, hepatic encephalopathy is a complication of advanced cirrhosis [52; 54; 55]. Lactulose and antibiotics may be used to manage these patients.

Injection sclerotherapy, an alternative long-term control measure, may be performed as a bedside procedure. The patient can be sedated using diazepam (Valium), meperidine hydrochloride (Demerol), propofol, fentanyl (Sublimaze), midazolam (Versed), or ketamine (Ketalar). The medications used are at the discretion of the anesthesia provider and surgeon based on the patient's medical history. It is important to be familiar with each, along with their respective reversal agents [57; 58]. Sclerosing solutions are then injected directly into the bleeding varices by means of fiberoptics endoscopy. Potential complications include chest pain, transient fever, ulceration of the injection sites, and formation of strictures. Most are self-resolving; strictures may be treated by dilatation. Perforation, a major complication, is rare. If perforation does occur, it is treated by keeping the patient NPO, suctioning gastric contents, and administering antibiotic therapy; surgery is seldom required [52; 55; 56].

Prophylactic antibiotics are also administered to lower rates of infection, death, and early rebleeding. IV ceftriaxone has demonstrated the most positive results in randomized controlled trials [52].

Specific Nursing Measures

It is important to emphasize that patients with cirrhosis must abstain from alcohol. Because cirrhosis is a chronic condition, most nursing interventions will be related to the patient's comfort. Teaching patients and the public about the effects of alcohol may have preventive benefits [59; 60; 61; 62].

Nursing measures for patients with esophageal hemorrhage include explaining treatments to the patient and assessing frequently to determine whether hemorrhage has ceased. As with any hemorrhage, the nurse is responsible for monitoring blood replacement therapy and administering vitamin K, as ordered. Bleeding esophageal varices create a crisis for patient and family. Timely explanations of ongoing interventions and anticipated results will help the patient cope with panic and fear of death. Providing nursing care in a decisive, supportive manner helps the patient regain control and to participate in the therapy. To provide optimum crisis care, the nurse should assess the family support structure and provide information and support to significant others as well as the patient. Fluid restrictions are generally maintained at 1,000 mL per 24-hour period [59; 60; 61].

ALCOHOL-INDUCED LIVER DISEASE

The spectrum of alcoholic liver disease incudes fatty liver disease, alcoholic hepatitis, and cirrhosis. Most deaths from alcoholic cirrhosis are attributable to liver failure, bleeding esophageal varices, or kidney failure. It has been estimated that there are 14 million persons in the United States with alcohol use disorder, and approximately 10% of those with

alcohol use disorder develop cirrhosis with continued heavy drinking [64; 65; 68].

Portal Cirrhosis

What are the characteristic signs/symptoms of portal cirrhosis?

The metabolism of alcohol leads to chemical attack on certain membranes of the liver. But whether the damage is caused by acetaldehyde or other metabolites is unknown. Acetaldehyde is known to impede the mitochondrial electron transport system, which is responsible for oxidative metabolism and generation of ATP; as a result, the hydrogen ions that are generated in the mitochondria are shunted into lipid synthesis and cytogenesis. Abnormal accumulations of these substances are found in hepatocytes (fatty liver) and blood. Binding of acetaldehyde to other molecules impairs the detoxification of free radicals and synthesis of proteins. Acetaldehyde also promotes collagen synthesis and fibrogenesis. The lesions of hepatocellular injury tend to be most prevalent in the centrilobular area that surrounds the central vein, where the pathways for alcohol metabolism are concentrated. This is the part of the lobule that has the lowest oxygen tension; it is thought that the low oxygen concentration in this area of the liver may contribute to the damage [64; 65].

The amount of alcohol required to produce chronic liver disease varies widely, depending on body size, age, sex, and ethnicity, but the high end of the range is about 80 g/day for 10 to 12 years. This amount of alcohol can be in the form of 8 ounces of 86 proof (41% alcohol) whiskey, two bottles of wine, or six 12-ounce bottles of beer. Even after alcohol intake has stopped and all alcohol has been metabolized, the processes that damage liver cells may continue for many weeks and months. Clinical and chemical effects often become worse before the disease resolves. The accumulation of fat usually disappears within a few weeks, and cholestasis and inflammation also subside with time. However, fibrosis and scarring remain. The liver lobules become distorted as new liver cells regenerate and form nodules [64; 65].

Although the mechanism by which alcohol exerts its toxic effects on liver structure is somewhat uncertain, the changes that develop can be divided into three states: fatty changes, alcoholic hepatitis, and cirrhosis [65].

Fatty liver is characterized by the accumulation of fat in hepatocytes, a condition called steatosis. The liver becomes yellow and enlarges as a result of excessive fat accumulation. The pathogenesis of fatty liver is not completely understood and can depend on the amount of alcohol consumed, dietary fat content, body stores of fat, hormonal status, and other factors. There is evidence that ingestion of large amounts of alcohol can cause fatty liver changes even with an adequate diet. The fatty changes that occur with the ingestion of alcohol usually do not produce symptoms and are reversible after the alcohol intake has been discontinued [65; 68].

Alcoholic hepatitis is the intermediate state between fatty changes and cirrhosis. It often is seen after an abrupt increase in alcohol intake and is common in binge drinkers. Alcoholic hepatitis is characterized by inflammation and necrosis of liver cells. This stage usually is characterized by hepatic tenderness, pain, anorexia, nausea, fever, jaundice, ascites, and liver failure, but some people may be asymptomatic. The condition is always serious and sometimes fatal, with an associated mortality rate of 34%. The immediate prognosis correlates with severity of liver cell injury. In those who continue to drink, the acute phase often is followed by persistent alcoholic hepatitis with progression to cirrhosis in a matter of one to two years [65; 68].

According to the American Association for the Study of Liver Diseases, because abstinence is the single most important factor in improving survival from alcohol-associated liver disease, multidisciplinary management with addiction specialists and referral to treatment for alcohol use disorder, particularly in patients with moderate to severe alcohol use disorder or clinically evident liver disease, is mandatory.

(https://journals.lww.com/hep/fulltext/2020/01000/diagnosis_and_treatment_of_alcohol_associated.25.aspx. Last accessed August 12, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

Alcoholic Cirrhosis

Alcoholic cirrhosis and malnutrition is the end result of repeated bouts of drinking-related liver injury and designates the onset of end-stage alcoholic liver disease. The gross appearance of the early cirrhotic liver is one of fine, uniform nodules on its surface. The condition has traditionally been called monocular or Laënnec cirrhosis. With more advanced cirrhosis, regenerative processes cause the nodules to become larger and more irregular in size and shape. As this occurs, the nodules cause the liver to become relobulized through the formation of new portal tracts and venous outflow channels. The nodules may compress the hepatic veins, curtailing blood flow out of the liver and producing portal hypertension, extrahepatic portosystemic shunts, and cholestasis [64; 65; 69].

METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

What is the cause of MASLD?

Metabolic dysfunction-associated steatotic liver disease (MASLD) was previously referred to as nonalcoholic fatty liver disease (NAFLD) but was renamed in 2023 to better reflect the underlying pathophysiology and embrace affirmative, nonstigmatizing terminology [70]. It is caused by metabolic dysfunction that affects the liver. As noted, in the United States, it is

the most frequently occurring form of chronic liver disease. The condition can range from simple steatosis (fatty infiltration of the liver) to nonalcoholic steatohepatitis (steatosis with inflammation and hepatocyte necrosis). Although steatosis alone does not appear to be progressive, approximately 10% to 15% of people with nonalcoholic steatohepatitis progress to cirrhosis. Obesity, type 2 diabetes, metabolic syndrome, and hyperlipidemia are coexisting conditions frequently associated with fatty liver disease. The condition is also associated with other nutritional abnormalities, surgical conditions, drugs, and occupational exposure to toxins. Both rapid weight loss and parenteral nutrition may lead to MASLD. Jejunoileal bypass, a surgical procedure historically used for weight loss, has largely been abandoned for this reason [65; 71].

Pathogenesis

The pathogenesis of MASLD is thought to involve both lipid accumulations with hepatocytes and formation of free radicals, in a manner similar to that which occurs with alcohol metabolism. The primary metabolic abnormalities leading to lipid accumulation are poorly understood but are thought to include alteration in pathways for uptake, synthesis, degradation, or secretion of hepatic lipids and resulting from insulin resistance. Obesity increases the synthesis and reduces the oxidation of free fatty acids. Type 2 diabetes or insulin resistance also increases adipose tissue lipolysis and the subsequent production of free fatty acids. When the capacity of the liver to export triglyceride is exceeded, excess fatty acids contribute to the formation of fatty liver. Abnormal lipid peroxidation ensues, followed by direct hepatocyte injury, release of toxic byproducts, inflammation, and fibrosis [65; 71].

Clinical Manifestations

MASLD is usually asymptomatic, although fatigue and discomfort in the right upper quadrant of the abdomen may be present. Mildly to moderately elevated serum levels of AST, ALT, or both are the most common and often the only abnormal laboratory findings. Other abnormalities, including hypoalbuminemia, a prolonged prothrombin time, and hyperbilirubinemia, may be present in persons with cirrhotic-stage liver disease. The diagnosis of MASLD requires the presence of >5% macrovesicular steatosis, inflammation, and liver cell ballooning, typically with a predominantly centrilobular distribution; this is usually demonstrated by imaging. Exclusion of alcohol as a cause of the disorder is also required [65; 72].

Treatment

The aim of treatment is to slow progression of MASLD and to prevent liver-related illness. Weight loss and exercise improve insulin resistance and are recommended in conjunction with treatment of associated metabolic disturbances. Alcohol use should be avoided. Disease progression is slow and the magnitude of disease-related morbidity and mortality is uncertain. One study has shown the use of statins and antioxidants such as vitamins A and E have been effective in reducing the odds of hepatic steatosis in patients with MASLD. Liver transplantation is an alternative for some with end-stage liver disease, but MASLD may reoccur in up to 39% of people post-liver transplantation [65; 72; 73; 74].

In adults with MASLD, the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO) recommend dietary and behavioral therapy-induced weight loss to improve liver injury, as assessed histologically or noninvasively.

(https://www.journal-of-hepatology.eu/article/S0168-8278(24)00329-5/fulltext. Last accessed August 12, 2024.)

Level of Evidence/Strength of Recommendation: 1, Strong Recommendation, Strong Consensus

INTRAHEPATIC BILIARY DISORDERS

Intrahepatic biliary diseases disrupt the flow of bile through the liver, causing cholestasis and biliary cirrhosis. Among the causes of intrahepatic biliary diseases are primary and secondary biliary cholangitis [55].

Primary Biliary Cholangitis

Primary biliary cholangitis (PBC), formerly primary biliary cirrhosis, is a chronic disease of the liver characterized by the autoimmune destruction of intrapolar bile ducts causing cholestasis. The disease is seen most commonly in women 40 to 60 years of age. Familial occurrences of the disease are found between parents and children and among siblings. With the possible exception of a reportedly higher risk of a polymorphism of the gene for the vitamin D receptor, there are no clear genetic influences for the disorder. As with other autoimmune disorders, possible environmental triggers include infections and chemical agents [63].

Clinical Manifestations

Primary biliary cholangitis is characterized by an insidious onset and progressive scarring and destruction of liver tissue. The liver becomes enlarged and takes on a green hue because of the accumulated bile. The earliest symptoms are unexplained pruritus, weight loss, and fatigue, followed by dark urine and pale stools. Osteoporosis occurs in 51% of women with the disorder. Jaundice is a late manifestation of the disorder, as are other signs of liver failure. Serum alkaline phosphatase levels are typically elevated [63].

Diagnosis and Treatment

What is the usual treatment of primary biliary cholangitis?

Diagnosis of primary biliary cholangitis is made when two of the following signs and symptoms are present [63]:

- Destruction of bile ducts and presence of nonsuppurative cholangitis on liver biopsy
- Cholestasis with alkaline phosphatase elevation for at least six months
- Presence of serum antimitochondral antibodies

Treatment is largely symptomatic. Ursodeoxycholic acid (ursodiol), the only drug approved for treating primary biliary cholangitis, increases bile flow, decreases the toxicity of bile contents, and has been shown to decrease the rate of clinical deterioration. Cholestyramine, a bile acid-binding drug, may prove beneficial for treatment of pruritus. Colchicine, which acts to prevent leukocyte migration and phagocytosis, and methotrexate, a drug with immunosuppressive properties, have also resulted in reported benefits in terms of symptom relief. Corticosteroids have been shown to improve liver histology and serum liver function tests, but are associated with serious long-term side effects. Liver transplantation remains the only effective treatment for advanced disease. Primary biliary cirrhosis does not recur after liver transplantation if appropriate immunosuppression is used [63].

Secondary Biliary Cholangitis

Secondary biliary cholangitis results from prolonged obstruction of the extrabiliary tree. The most common cause is cholelithiasis. Other causes of secondary biliary cirrhosis are malignant neoplasms of the biliary tree or head of the pancreas and strictures of the common duct caused by previous surgical procedures. Extrahepatic biliary cholangitis may benefit from surgical procedures designed to relieve the obstruction. The presence of dark urine is a sign that indicates emergent medical attention is necessary [64; 66; 67].

INFECTIOUS AND INFLAMMATORY DISORDERS

Infectious and inflammatory disorders of the hepatobiliary system can involve the liver or the gallbladder. Hepatic infections may be associated with inflammation of hepatic cells, hyperplasia of Kupffer cells, bile stasis, or tissue necrosis. Biliary inventions may be associated with dilation of the gallbladder, which will be filled with bile, pus, and blood. Although the signs and symptoms of different types of hepatitis are much the same, the major symptom present for all is anorexia [75; 76; 77].

TOXIC AND DRUG-INDUCED HEPATITIS

Certain agents, including carbon tetrachloride, yellow phosphorus, and acetaminophen (in large doses), are hepatotoxins. When ingested or inhaled, they cause necrosis of hepatic cells. Hepatitis related to these substances is called toxic hepatitis [76; 78].

Varying patterns of hepatic dysfunction are seen in response to use of other drugs and anesthetic agents. For example, halothane, methyldopa, and isoniazid can produce hepatitis. Chlorpromazine, erythromycin estolate, and methimazole can cause intrahepatic cholestasis with jaundice. Phenylbutazone and the sulfonamides can produce granulomas within the liver [76; 78].

Clinical Manifestations

Both drug-induced and toxic hepatitis are manifested by inflammation of hepatic cells, hyperplasia of Kupffer cells, and bile stasis; however, toxic hepatitis is also associated with acute cellular necrosis. The onset of both forms is similar to that of viral hepatitis from which they must be quickly distinguished if detoxification is to be initiated. Anorexia, jaundice, and hepatomegaly are common. In toxic hepatitis, the illness may progress rapidly, with rising fever, subdermal hemorrhage, and severe vomiting. Delirium, coma, and convulsions develop, and the patient dies within a few days. If the toxin is promptly identified and exposure is discontinued, however, the patient may recover quite rapidly. Cirrhosis sometimes develops after recovery [76; 78].

Drug-induced hepatitis may develop after repeated exposures have sensitized the patient to a drug. For this reason, any medication that causes pruritus or other symptoms of sensitivity should be immediately withdrawn and the sensitivity noted on the patient's record. Chills, fever, rash, pruritus, arthralgia, and nausea are early signs of drug-induced hepatitis. Icterus, hepatomegaly, and hepatic tenderness follow. The urine is dark. Symptoms may subside once the drug is withdrawn, but drug-induced hepatitis may be fatal, and postnecrotic cirrhosis also may develop [78; 79; 80; 81]. The anesthetic agent halothane has been linked to episodes of drug-induced hepatitis; therefore, anesthetics should be rotated for patients undergoing repeated surgical procedures [81].

Therapeutic and Specific Nursing Measures

Treatment is directed at the removal of the toxin or sensitizing agent, if known. Early diagnosis is important. The history can yield useful findings regarding exposure to toxins or medications. Attention should focus on occupational history, possible exposure to hepatotoxins during hobby activities (e.g., furniture finishing), and medication history, including over-the-counter medications and self-prescribed vitamin therapy. Once the disease has been diagnosed, nursing care focuses on comfort measures and the replacement of blood, fluids, and electrolytes [75; 78].

HEPATIC ABSCESS

Hepatic abscess is an invasion of the liver by micro-organisms producing a localized collection of pus in a cavity formed by destruction of tissue. Hepatic abscess may be caused by fungal, bacterial, or even protozoan infection. An infection anywhere in the body can lead to formation of an hepatic abscess, but gastrointestinal infections are especially likely to do so [75; 76; 82; 83].

Usually, micro-organisms that invade the liver are destroyed by the phagocytic Kupffer cells, but occasionally a few survive. The lobular structure of the liver tends to keep the infection small and circumscribed, but several lobules may be affected. As the micro-organisms multiply, the toxins they produce destroy hepatic cells. Concurrently, the body's defense system acts to destroy the invading organisms, and the cavity becomes filled with a mixture of leukocytes, micro-organisms, and dead and necrotic hepatic cells [75; 76].

Clinical Manifestations

Patients with hepatic abscess will have a high fever and a painfully enlarged liver, anemia, elevated WBC levels, and icterus. As the temperature rises, the patient has alternating episodes of chills and diaphoresis; toxic shock can occur within hours. If identified soon enough, the infective agent can be controlled with antimicrobial therapy. Sometimes, septicemia cannot be reversed, and the patient dies [76].

Therapeutic Measures

Non-aspirin analgesics, intravenous fluid therapy, and parenteral antimicrobial agents may be prescribed. Occasionally, surgical intervention may be indicated to drain large abscessed areas or to resect an abscessed portion of the liver. This is done rarely, however, because coagulation abnormalities associated with liver dysfunction increase the risk of severe hemorrhage. The most common surgical intervention is percutaneous drainage. This may be done intermittently, or continuous catheter drainage may be employed [76].

Specific Nursing Measures

Continual assessment is a crucial part of nursing care. A patient history should include inquiry regarding recent (within past six months) infection and presence of diabetes or insulin resistance [20].

Hourly monitoring of temperature and vital signs may be required to estimate whether the patient is becoming septic or whether antimicrobial therapy is taking effect. Hepatic abscess is accompanied by pain and fever, so supportive care with comfort measures is necessary. If surgical intervention is indicated or drainage initiated, the nurse will teach the patient about the procedure, provide reassurance, and assess for hemorrhage [20].

VIRAL HEPATITIS

Hepatitis is an inflammatory state of the liver and may be caused by exposure to toxic chemicals, autoimmune disease, fatty liver disease, or infection. Many common viral infections in humans are associated with mild, usually transient, secondary inflammation of the liver. The term "viral hepatitis" is applied to infection caused by a set of viruses unique in their primary trophism for the liver and their propensity to cause serious, often prolonged "primary" hepatitis. For clinical purposes, the viruses causing primary hepatitis are grouped and classified alphabetically in accordance with when each was identified: hepatitis A, B, C, D, and E. In 1994, hepatitis F was identified as a cause of fulminant liver failure [84]. This was later found to be a variant subspecies of another virus. Therefore, "F" is now omitted in the hepatitis alphabet. A virus similar in structure to hepatitis C was initially designated hepatitis G; however, this virus has been reclassified as a Pegivirus GB virus-C (GBV-C) [85]. This virus can cause subclinical infection in humans but is not linked to active disease.

Hepatitis A

How is hepatitis A virus transmitted?

The World Health Organization (WHO) estimates the annual worldwide incidence of hepatitis A to be 1.5 million per year [86]. Within the United States, diagnosed cases of hepatitis A virus must be reported to the local health authorities, who in turn report the incidence to the Centers for Disease Control and Prevention (CDC). Many persons who contract hepatitis A virus, however, do not have clinical symptoms. Therefore, the CDC must estimate the actual incidence of hepatitis A virus infection based upon CDC reports and projections. For the 10-year period 1999 to 2009, the CDC estimates that 749,000 cases occurred within the United States [87].

Since the introduction of hepatitis A vaccine in 1995, the incidence of hepatitis A in the United States has declined by 95% [87]. However, after falling to a low of 1,239 cases reported in 2014, a series of outbreaks from 2013 to 2023 resulted in a dramatic increase in cases, reaching 12,474 reported cases in 2018 and 18,846 in 2019 [88]. According to the CDC, the increase in incidence was primarily the result of contaminated organic fruit, including strawberries, pomegranate seeds, blackberries, and a mixed antioxidant blend [88].

Hepatitis A is transmitted via the fecal-oral route, most commonly from contaminated water or food. After the virus is ingested, it is transported from the intestines to the liver, where it invades the hepatocytes. The virus uses the hepatocytes for viral replication and is then released into the bloodstream and excreted in the stool. HAV that is acquired percutaneously travels directly from the bloodstream to the liver to invade the hepatocytes; viral replication and excretion follow the same pattern as in fecal-oral transmission.

Clinical Manifestations

Signs and symptoms of hepatitis A infection can vary from subclinical disease to fulminant (sudden and intense) illness. In symptomatic patients, the incubation period (i.e., time from exposure to onset of illness) is in the range of 15 to 50 days (average: 28 days). Clinical symptoms and signs include nausea, vomiting, headache, fever, chills, abdominal discomfort, hepatomegaly, and right upper quadrant tenderness. For most patients, symptoms are mild and subside in three to seven days. Others will have more significant disease and will progress to an icteric phase (jaundice). For these patients, recovery typically occurs after about three weeks.

Fulminant infection occurs in less than 1% of the cases. Some of these patients may have such severe damage that they require a liver transplant. Fatalities from hepatitis A are extremely rare. There is no known chronic carrier state.

Laboratory studies reflect leukopenia, atypical lymphocytes, and elevated ALT and AST levels. As discussed, anti-HAV IgM can be detected early in the disease, usually appearing in detectable levels 2 to 3 weeks after exposure, then declining to undetectable levels in 12 to 24 weeks. IgG levels begin to rise three to four weeks after exposure and remain elevated throughout life.

Therapeutic Measures and Prevention

Treatment of HAV is supportive and directed at maintaining adequate nutrition and controlling symptoms. Ingestion of alcohol and/or hepatotoxic medications is avoided. For patients with fulminant hepatic failure resulting from HAV, corticosteroids may be used. However, clinical research has not demonstrated improved outcomes in patients receiving corticosteroids when compared with those who did not receive steroid treatment [89].

As with any other disease, prevention is the most effective strategy. Hepatitis A vaccine is licensed in the United States for use in individuals 1 year of age and older. Immunoglobulin (Ig) can provide short-term protection, both pre- and post-exposure (administered within two weeks after exposure for maximum protection).

The U.S. Food and Drug Administration (FDA) has approved two single-antigen HAV vaccines and one combination vaccine for use in the United States, all of which are inactivated vaccines. The single-antigen vaccines are Havrix and VAQTA. Both are administered to adults in a dose of 1 mL intramuscularly. The dose for children is 0.5 mL [90]. Single-antigen vaccines are considered interchangeable. A second dose of either vaccine can be administered, regardless of which vaccine was administered as the first dose.

An alternative to single-antigen HAV vaccines is Twinrix, which contains inactivated HAV and HBV recombinant vaccines. It is immunogenic against HAV and HBV but requires three injections of 1 mL intramuscularly. The suggested schedule is an initial injection followed by boosters at one and six months. This vaccine is not approved for use in children. Immunity is expected to persist for at least 20 years (and possibly longer) in those who receive all three doses [90; 91].

Passive immunization with human Ig, preferably administered within two weeks of known or anticipated exposure, provides short-term protection against HAV infection for persons who have not been vaccinated. The single human Ig product licensed for hepatitis A prophylaxis in the United States is GamaSTAN S/D.

Sanitation strategies are also important in controlling HAV. If in water, the virus is inactivated by boiling the water for five minutes. Hand hygiene using alcohol-based hand sanitizers containing 60% to 95% ethanol are ineffective against HAV, even when in contact with the virus for a full two minutes [92; 93]. Therefore, handwashing with soap and water for at least 20 seconds is recommended rather than hygiene using hand sanitizers. If handwashing with soap and water is not an option, cleansing the hands with povidone-iodine for at least 30 seconds may be considered.

Specific Nursing Measures

Persons with hepatitis A may often be cared for at home. Hospitalized patients will require enteric isolation and interventions for alternation in comfort (pruritus and pain), nutritional intake, and fluid volume; impairment of skin integrity and O_2/CO_2 exchange; and disturbances in self-concept. Persons giving care in the home should wear gloves if contact with feces is possible. Gowns should be worn in any situation in which gross soiling occurs. Careful attention to handwashing is essential for patients and for those giving care [95].

Discharge planning for hospitalized patients includes encouraging the patient to get ample rest, ingest a well-balanced diet, and avoid alcohol and over-the-counter medications for at least six months. There is no chronic carrier state with hepatitis A. The patient will not progress to chronic hepatitis or cirrhosis [95].

Hepatitis B

The hepatitis B virus is one of the smallest viruses known to cause disease in animals. Ten HBV genotypes, labeled A through J, and 30 subtypes have been identified [96]. The genotype of the virus influences the likelihood of developing cirrhosis and the response of the virus to therapy with interferon.

HBV consists of a core and an envelope. The envelope contains HBsAg proteins, glycoprotein, and lipids. The core of HBV includes viral DNA, enzymes necessary for replication, and antigenic protein particles distinctly different from those found in the envelope. The viral DNA is circular and predominantly double stranded, but with a single-stranded arc. The core antigen is termed HBcAg.

HBV is a bloodborne pathogen that is typically acquired parenterally, perinatally, or through sexual interaction. As with HIV infection, sexual contact and use of contaminated needles for drug injection are the primary risk factors for HBV [97]. However, HBV is considered 50 to 100 times more infectious than HIV, requiring a much smaller inoculum for transmission. Thus, a needlestick injury from a source patient who is coinfected with both HBV and HIV is more likely to transmit HBV, even when the needle is solid (e.g., a suture needle) and even when blood is not visible. Because HBV does not transfer across the placenta, perinatal transmission occurs when an infant is exposed to the blood of an infected mother at the time of delivery. Parenteral exposures include occupational exposure of healthcare workers (1%), use of injected drugs (15%), tattoos, ear and body piercing, acupuncture, and blood transfusions received prior to 1980. Rare cases of transfusion-associated HBV continue to occur, indicating that the virus was present in the blood but with antigen levels below the level of laboratory detection [98].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force recommends screening for hepatitis B virus infection in adolescents and adults at increased risk for infection.

(https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-b-virus-infection-screening. Last accessed August 12, 2024.)

Strength of Recommendation: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

Clinical Manifestations

The incubation period for HBV can be as little as 45 days or as long as 180 days, but most commonly is 60 to 90 days. The severity of primary HBV infection varies from subclinical to fulminant illness. The age of the patient, the integrity of the immune system, and the infecting dose of the virus influence the severity of acute disease. Persons younger than 5 years of age exhibit mild symptoms or no symptoms, while 70% of infected adults exhibit significant clinical symptoms [99].

Signs and symptoms associated with acute HBV infection are similar to those of other acute viral hepatitis syndromes and include malaise, nausea, abdominal discomfort, icterus, and dark urine. Physical examination of the patient typically reveals an enlarged, tender liver and a yellowish hue to the skin. The spleen is palpable in some patients. In patients with fulminant hepatitis, progressive signs of hepatic encephalopathy (e.g., somnolence, confusion, stupor, coma) are common.

Therapeutic Measures

There is no specific treatment for acute HBV infection; management is primarily supportive. Control of nausea and vomiting, maintenance of fluid and electrolyte balance, avoidance of potentially hepatotoxic drugs and alcohol, and extended periods of rest are the typical therapies.

In less than 1% of cases, fulminant acute liver failure develops. Treatment for fulminant hepatic failure includes compensating for coagulation defects, correcting acid-base as well as fluid and electrolyte disturbances, prevention of hypoglycemia, administering prophylactic antibiotics, and therapies to reduce ammonia levels and combat cerebral edema. With aggressive therapy, improved intensive care and the use of orthotopic liver transplantation, the mortality rate for fulminant acute hepatic failure has gone down to 40% [100].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Association for the Study of Liver Diseases (AASLD) recommends antiviral therapy for adults with immune-active chronic hepatitis B infection (hepatitis Be antigen negative or positive) to decrease the risk of liver-related complications.

(https://journals.lww.com/hep/pages/articleviewer.aspx?year=2018&issue=04000&article=00034&type=Fulltext. Last accessed August 12, 2024.)

Level of Evidence/Strength of Recommendation: Moderate/Strong

Preventive Measures

As with hepatitis A, prevention is the best method for dealing with hepatitis B. Hepatitis B vaccine has been available since the 1980s and has been recommended as a routine childhood immunization since the early 1990s. Hepatits B vaccine is available in the United States in seven different formulations. Of those seven formulations, only Engerix-B and Recombivax-HB are approved for neonates and in pregnancy. Other HBV vaccines include Heplisav-B and PreHevbrio. Combination vaccines that include HBV vaccine in the formulation include Twinrix (providing immunization against HAV and HBV), Pediarix (containing diphtheria toxoid, tetanus toxoid, acellular pertussis antigens, recombinant HBsAg, and inactivated poliovirus) and Vaxelis (containing diphtheria toxoid, tetanus toxoid, acellular pertussis antigens, inactivated poliovirus, recombinant HBsAg, and *Haemophilus influenzae* type b) [99].

Hepatitis B vaccine is typically administered as a series of three intramuscular injections, the second and third doses given at one month and six months, respectively, after the first dose [99]. In 2017, a two-dose series hepatitis B vaccine for unvac-

cinated or incompletely vaccinated individuals 18 years of age and older was approved by the FDA [101; 102]. In addition, evidence has indicated that two injections may be sufficient to achieve protection if administered in adolescence [99]. The ACIP recommends all adults 19 to 59 years of age and adults 60 years of age and older with risk factors for hepatitis B infection should receive hepatitis B vaccination [103]. Hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) should be administered to infants weighing at least 2,000 grams born to persons with hepatitis B infection within 12 hours of birth, followed by completion of the vaccine series and postvaccination serologic testing. These neonates should receive hepatitis B vaccination within 24 hours of birth, followed by completion of the vaccine series. If the HBsAg-exposed neonate weighs less than 2,000 grams, the first dose of vaccine should not be counted as part of the three-dose series. Instead, the series is administered when the infant attains a weight of 2,000 grams or 1 month of age, whichever comes first, and at 2 and 7 months of age. All unvaccinated children and adolescents younger than 19 years of age also should receive the vaccine [94].

Persons who have not been immunized (or did not respond to the vaccine) and are exposed to hepatitis B virus may achieve passive protection from infection by receiving HBIG within seven days of exposure. The usual dose of HBIG is 0.06 mL/kg. For persons who have not been immunized, an accelerated schedule of immunizations is recommended following the dose of HBIG. For documented nonresponders, a second dose of HBIG is appropriate.

Strict adherence to Standard Precautions is recommended in order to prevent exposure to hepatitis B virus or other bloodborne pathogens. Careful handling of needles is also imperative. Because of the hardiness of HBV even in adverse conditions, caution should be used when cleansing objects contaminated with blood or body secretions, regardless of whether or not the body fluids have dried.

Hepatitis B can be inactivated on surfaces with the use of 1:10 bleach solution or hospital-grade disinfectant. Unlike hepatitis A virus, alcohol-based hand sanitizers, used for 30 seconds, are effective against HBV [92].

Hepatitis C

HCV is a single-stranded RNA virus, with properties similar to those of the flaviviruses, a genus of the family of Flaviviridae that includes yellow fever and St. Louis encephalitis viruses. The genome contains a single open reading frame that encodes a polyprotein of about 3,000 amino acids. The transcript is cleaved into single proteins, including three structural proteins (one core and two envelope proteins) and four nonstructural proteins. The virus is genetically unstable, which leads to multiple genotypes and subtypes.

HCV is considered a bloodborne pathogen. The most common source of infection is percutaneous or parenteral exposure through transfusion, use of injectable drugs, and occupational injury of healthcare providers with a contaminated sharp object. The blood supply in the United States has been tested for hepatitis C since the early 1990s. Now that more advanced screening tests for HCV are used in blood banks, the risk is considered to be less than 1 chance per 2 million units transfused [104]. Therefore, the annual incidence rate of HCV transmission from transfusion therapy since 1994 is less than one case per 100,000 population. In 2016, the CDC issued a health advisory due to an increasing number of acute HCV infections among persons undergoing hemodialysis [105].

Hepatitis C virus is the leading cause of end-stage liver disease and the leading reason for liver transplantation in the United States [104; 106]. Chronic HCV infection has also been associated with membranoproliferative glomerulonephritis, cryoglobulinemia, and B-cell lymphoma [104]. Coinfection of HCV with HIV occurs in 50% to 90% of persons who acquired HIV through injection drug use [107].

HCV occurs throughout the world, with endemic rates varying widely. The WHO estimates that 10% of the population of the Middle East, Africa, and Eastern Europe are infected with HCV. In the United States, an estimated 1.8% of the population (approximately 4 million people) is infected with HCV, and only about half of those infected are aware that they are. Rates of HCV in the United States have increased dramatically since 2010. This has been primarily attributed to the nation's opioid crisis and increased infection among injecting drug users. In 2021, 5,023 new cases of acute HCV were reported, an increase of 492% since 2010 and 129% since 2014 [108]. After adjusting for under-ascertainment and under-reporting, an estimated 69,800 acute hepatitis C cases occurred in 2021 [108]. In addition, 107,540 cases of newly identified chronic hepatitis C were reported in 2021 [108].

The U.S. Preventive Services Task Force recommends screening for hepatitis C virus infection in adults 18 to 79 years of age. (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening. Last accessed August 12, 2024.)

Strength of Recommendation: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

Clinical Manifestations

The incubation period for HCV varies widely, from a mean of 7 to 10 weeks and a range of 2 to 20 weeks. HCV antibody is detectable in 80% of cases 15 weeks after exposure and in 97% of cases by 6 months after exposure. People with recently acquired acute infection typically have detectable HCV RNA levels as early as one to two weeks after exposure to the virus [104]. During the acute phase of the infection, 60% to 70% of HCV positive persons will be asymptomatic; approximately 20% of patients will develop mild jaundice, and the remaining persons will have generalized nonspecific symptoms, such as anorexia, nausea, fatigue, malaise, and abdominal pain. During this phase, serum ALT and AST levels are elevated then return to normal range. Fulminant acute hepatitis associated with HCV is rare [100; 109].

After the acute infection, 15% to 25% of patients will demonstrate an absence of HCV RNA in the serum and normalization of liver enzymes, within six months indicating resolution of the infection and clearance of the virus from the body. The presence of detectable HCV RNA in persons who test positive for HCV antibody is 74% in the general population. However, the rate of progression to chronic infection is higher in some subpopulations. In particular, the progression rate is more than 90% in African American individuals and as high as 98% in African American men. In those persons in whom HCV RNA remains detectable, indicating continued presence of the virus, 30% to 40% will maintain normal ALT levels and will show no evidence of chronic liver disease. The remaining 60% to 70% of chronically infected patients will have fluctuating ALT levels indicative of chronic liver disease and risk of subsequent progression to cirrhosis. On rare occasions, a patient will demonstrate positive HCV RNA without the presence of HCV antibody. Therefore, in a patient who exhibits chronic hepatitis without apparent cause, assessment of HCV RNA may be indicated [104; 110].

Chronic hepatitis from HCV infection usually progresses slowly, with cirrhosis developing in 20% to 25% of patients over a period of 20 to 30 years. However, persons with HCV infection whose daily ethanol consumption exceeds 50 g (about 3.5 standard drinks) per day are twice as likely as nondrinkers to develop cirrhosis and progress to cirrhosis more quickly (in as little as 10 years) [111]. Of those with cirrhosis, 25% eventually develop hepatocellular carcinoma. Persons who ingest alcohol or who were older than 40 years of age at the onset of infection have a more rapid progression of cirrhosis. Men have a higher incidence of cirrhosis than women. Persons with MASLD and those receiving immunosuppressive therapy are also more likely to progress to cirrhosis [112].

Because acute HCV infection can be asymptomatic, the first indication of the presence of chronic HCV infection may be elevated liver enzymes on laboratory testing obtained in connection with another clinical condition or routine health examination. In evaluating the cause of liver enzyme elevation, a hepatitis panel is typically ordered. Testing for the presence of HCV RNA has become the accepted method of confirming current HCV infection (acute or chronic) [104]. Qualitative HCV RNA testing determines whether or not hepatitis C viral particles are present in the blood and can therefore differentiate between resolved and continued infection. Quantitative HCV RNA testing evaluates the amount of hepatitis C virus in the blood and can be used to guide therapy [104; 113]. In most commercial laboratories, a positive HCV antibody test triggers a reflex test for quantitative HCV RNA; qualitative HCV RNA is rarely performed.

Therapeutic Measures

Based upon genetic characteristics, eight genotypes and more than 90 different subtypes of HCV virus have been identified. Because the genotypes respond differently to therapy, genotypic testing should be performed for persons with chronic progressive HCV infection who are considering antiviral therapy [104]. In the United States, genotype 1 accounts for 60% to 75% of HCV infections and genotypes 2 and 3 account for about 25% [114].

The treatment of HCV infection has advanced rapidly following the introduction of anti-HCV protease inhibitors in 2011. These newer, direct-acting antiviral drug combinations are highly effective and relatively free of side effects; thus, therapy is now considered for virtually all patients diagnosed with HCV infection [115]. In order to provide healthcare professionals with timely guidance, the IDSA and the AASLD have developed evidence-based recommendations for the diagnosis and management of hepatitis C infection, last updated in 2023. However, due to the rapidly evolving nature of new therapies and other developments, the IDSA and the AASLD recommend reviewing current recommendations online, available at https://www.hcvguidelines.org [115].

The IDSA/AASLD 2023 guidelines emphasize that treatment is recommended for all patients with chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy [115]. Prior to treatment, patients should be educated regarding proper administration of medications, adherence, and prevention of reinfection. Pretreatment assessment to facilitate decision making regarding the treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (e.g., hepatocellular carcinoma screening) is recommended in all patients.

During treatment, routine laboratory monitoring of hepatic function or inflammation is not indicated in persons without advanced liver disease. Because of drug-drug interactions between warfarin and direct-acting antiviral therapy, periodic INR should be assessed for patients on warfarin in order to evaluate for subtherapeutic anticoagulation. Drug-drug interactions of direct-acting antiviral therapy and medications used to treat type 2 diabetes can lead to hypoglycemia. Thus, persons

on oral diabetes medications should be counseled about the potential for this interaction. No other laboratory studies are required for monitoring.

HCV quantitative RNA should be assessed 12 to 24 weeks after the conclusion of the recommended course of therapy. Persons with sustained virological response at 12 weeks or greater have less than 1% chance of re-emergence of the original infection. They can, however, become re-infected if high-risk practices are continued or re-initiated.

Achieving and maintaining SVR has positive effects on both hepatic and extrahepatic manifestations of HCV infection. These improvements include fibrosis regression, reduction in portal hypertension, reduction in the incidence of hepatocellular carcinoma, reduced incidence of myocardial infarction, reduced incidence of stroke, lower rate of insulin resistance and type 2 diabetes, improved quality of life, and lower all-cause mortality rate [116].

Even in compliant patients, treatment failures can occur. Factors that correlate with treatment failure include degree of fibrosis; the presence of advanced fibrosis in genotype 3 is particularly prone to treatment failure. Other factors that can affect treatment success include age older than 55 years, male sex, and Hispanic or Black ethnicity/race. Fortunately, prior treatment with interferon-based regimens does not usually prevent achieving SVR with direct-acting antiviral therapy. However, prior incomplete or inconsistent treatment with direct-acting antiviral therapy can lead to medication-resistant infection and treatment failure [117]. Patients who experience treatment failure should be referred to a specialist for retreatment. Monitoring of liver function should be continued by the specialist or primary care provider at least every six months until retreatment is initiated [115].

As noted, infants who are noted perinatally exposed to HCV should have HCV RNA testing at 2 to 6 months of age. Repeat HCV RNA testing, with genotype determination, should be performed when the child is 3 years of age. If viremia remains and genotype 1, 4, 5, or 6 is identified, a weight-based course of ledipasvir-sofosbuvir can be initiated, with an expected SVR in 98% of children. For children with genotype 1-6 and no evidence of fibrosis level 3 or 4, treatment with a weight-based dose of either sofosbuvir-velpatasvir or glecaprevir-pibrentasvir can be accomplished. After successful treatment with any of these three regimens, liver damage caused by HCV usually resolves and these children show no evidence or residual effects [115; 118].

For patients with cirrhosis secondary to chronic HCV or HBV infection that has gone untreated or failed therapy, liver transplantation may be indicated. Replacing the liver, however, does not cure the infection. The transplanted liver will also become infected, and immunosuppressive agents facilitate the progression of this infection. At present, chronic viral hepatitis is the most common diagnosis of persons receiving liver transplants in the United States [104].

Preventive Measures

There is no vaccine to prevent hepatitis C. The best way to prevent hepatitis C is by avoiding behaviors that can spread the disease, especially injecting drugs with non-sterile injection equipment. Hepatitis C can spread when a person comes into contact with blood from an infected person. Injecting drugs is the most common way HCV is transmitted in the United States. For people who inject drugs, community-based prevention programs, such as medication-assisted treatment and syringe services programs, can reduce the transmission of HCV.

Although the risk of sexual transmission of HCV is considered to be low, avoiding unprotected sexual exposure by using condoms has been shown to reduce the chance of sexually transmitted infections.

Hepatitis D

HDV is an RNA virus, the core of which is distinctively different from other viruses. However, due to a defect in replication, HDV is unable to synthesize a viral coat. It must borrow a coat from HBV in order to complete the replication process. Therefore, HDV cannot cause infection independently but instead must exist as a coinfection (acquired at the same time as HBV) or a superinfection (HDV acquired in a patient who is chronically infected with HBV). In the United States, the infection primarily occurs as a coinfection among intravenous drug users. In some areas of the world in which chronic HBV infection is endemic (including the Amazon Basin of South America, China, and Southeast Asia), HDV is more commonly a superinfection [119; 120].

Patients coinfected with HBV and HDV tend to have a more severe case of acute hepatitis. The mortality rate in coinfection has been reported to be as high as 20%. Superinfection with HDV results in rapid progression of cirrhosis, with 70% to 80% of coinfected individuals showing signs of liver failure, compared to 15% to 30% of patients with chronic HBV and no cirrhosis [121]. Prevention of HDV is accomplished through the same means as prevention of hepatitis B. A 12-month course of peginterferon alfa-2a is the recommended treatment for patients with elevated HDV-RNA levels and ALT elevation [96]. Nearly 25% of patients involved in an efficacy study of peginterferon alfa-2a treatment showed sustained clearance of HDV RNA over 48 weeks [122]. Given the limited efficacy of current therapies, it is reasonable to refer patients to specialized centers that offer access to experimental therapies for HDV [96]. Immunization against hepatitis B is effective prevention of HDV also because if the individual is immune to HBV, he/she cannot become infected with HDV. Avoidance of bloodborne pathogen exposure through observance of Standard Precautions is a primary mechanism of prevention for persons already chronically infected with HBV.

Hepatitis E

Like hepatitis A, hepatitis E virus is spread through the fecal-oral route, and like HAV, HEV was also first identified via electron microscope examination of stools of infected patients. HEV has been associated with outbreaks in India, Burma, Pakistan, Russia, China, northern and central Africa, Peru, and Mexico. Outbreaks are usually associated with a contaminated water supply. No outbreaks have occurred in the United States or Western Europe, though individual cases have been identified in persons who have recently traveled to areas in which the virus is endemic [119; 123].

HEV most often affects young adults. The incubation period is two to nine weeks, with an average of six weeks. Signs and symptoms are similar to HAV, but with a higher incidence of jaundice, which can be prolonged. The disease is self-limited in the majority of patients. The fatality rate in acute HEV is between 1% and 2%, except in pregnant women. In pregnant women with HEV infection, mortality can reach as high as 30% [123]. No cases of chronic liver disease associated with HEV have been reported.

The treatment of HEV is nonspecific and is directed toward supportive care. Because the incidence of HEV is low and most cases resolve without negative sequelae, the development of a vaccine against HEV has not been a priority for pharmaceutical companies or national and international health agencies. Primary preventive strategies, therefore, concentrate on improved sanitation [123; 124].

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is a severe type of chronic hepatitis that is associated with interface hepatitis, circulating autoantibodies, and hypergammaglobulinaemia. Although the disorder is usually seen in young women, it can occur in either sex at any age.

Clinical and laboratory observations have led to the hypothesis that autoimmune hepatitis is a multifactorial disorder, with genetic and environmental factors playing important roles. Most knowledge of the genetics of the disease comes from the human leukocyte antigen (HLA), located on the short arm of chromosome 6. The environmental agents assumed to induce autoimmune hepatitis have not been delineated but include viruses and chemical agents [126; 127].

Two distinct types of autoimmune hepatitis have been identified. Type 1 autoimmune hepatitis, the most common form of the disease, is characterized by increased levels of anti-smooth muscle and antinuciler autoantibodies. Approximately 78% of cases occur in women, and 38% of patients with autoimmune hepatitis also have other autoimmune diseases. Susceptibility to type 1 autoimmune hepatitis resides mainly with the *HLA-DRBI* gene.

Type 2 autoimmune hepatitis occurs mainly in children 2 to 14 years of age and is characterized by the presence of antibody to liver and kidney microsomes and liver cytosol. The disorder is often accompanied by other autoimmune disorders, especially type 1 diabetes, vitiligo, and thyroiditis. The genetic component for this type of autoimmune hepatitis is less well defined [126; 127].

Clinical Manifestations

Clinical manifestations of the disorder covers a spectrum that extends from no apparent symptoms to signs of inflammatory liver disease or cirrhosis. Physical examination may reveal no abnormalities but may also reveal hepatomegaly, splenomegaly, jaundice, and signs and symptoms of chronic liver disease. In asymptomatic cases, the disorder may be discovered when abdominal serum enzyme levels are identified during performance of routine screening tests [126; 127].

Diagnosis and Treatment

The differential diagnosis of autoimmune hepatitis includes measures to exclude other causes of liver disease, including hepatitis B and C. A characteristic laboratory finding is that of a marked elevation in serum gamma globulins [126; 127].

The American Association for the Study of Liver Diseases recommends that all patients with autoimmune hepatitis should be screened for celiac and thyroid diseases at diagnosis. Further, these patients should be assessed for rheumatoid arthritis, inflammatory bowel disease, autoimmune hemolytic anemia, diabetes, and other extrahepatic autoimmune diseases based on symptomatology and medical provider concern.

(https://journals.lww.com/hep/fulltext/2020/08000/diagnosis_and_management_of_autoimmune_hepatitis.24.aspx. Last accessed August 12, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

Corticosteroid and immunosuppressant drugs are the treatments of choice for this type of hepatitis. Although some people remain in remission after drug treatment is withdrawn, most require long-term maintenance therapy. Liver transplantation may be required for those who are refractory to or intolerant of immunosuppressive therapy and in whom end-stage liver disease develops. All hepatotoxic medications should be avoided, even analgesics such as acetaminophen [125; 126; 127].

CHOLECYSTITIS

Cholecystitis is an inflammation of the gallbladder, and it may be either acute or chronic. An acute inflammation may begin in the mucosal layer as a primary infection. More often, it is superimposed on a chronic infection initially related to cholelithiasis (also known as gallstones). The gallbladder becomes dilated and filled with bile, pus, and blood. Common infective organisms include staphylococci, streptococci, and enteric organisms [128; 129].

Clinical Manifestations

Major symptoms of cholecystitis are intense pain, tenderness, and rigidity in the right upper quadrant of the abdomen associated with nausea, vomiting, and the usual signs of inflammation. Jaundice and icteric color of the sclera may be present if there is an obstruction. If the gallbladder is filled with frankly purulent matter, the condition is called empyema of the gallbladder. Although chronic cholecystitis may be related to an acute attack, it is almost always associated with cholestasis. Stools may be clay colored due to a stone obstructing flow of bile [128; 129].

Therapeutic Measures

Laparoscopic cholecystectomy may be indicated after acute inflammation has been relieved by medical intervention. The condition typically resolves following treatment of cholelithiasis [128; 129].

NEOPLASTIC AND OBSTRUCTIVE DISORDERS

CANCER OF THE LIVER

There are two major types of primary liver cancers: hepatocellular carcinoma, which arises from the liver cells, and cholangiocarcinoma, which is a primary cancer of bile duct cells [125].

Hepatocellular Carcinoma

Hepatocellular cancer (HCC) accounted for 41,210 new cases of liver cancer in the United States in 2023, making it the most common form of liver cancer. Globally, HCC was identified as the cause for nearly 906,000 new liver cancer cases and 830,000 deaths in 2020 [130]. In recent decades, there has been increased incidence in developed countries as a consequence of chronic HCV infection, and the incidence in the United States has more than tripled since 1980. Although primary tumors of the liver are relatively rare in developed countries of the world, the liver shares with the lung the distinction of being the most common site of metastatic tumor [125].

Among the factors identified as etiologic agents in liver cancer are chronic viral hepatitis (HBV, HCV, HDV), cirrhosis, smoking, heavy alcohol consumption, obesity, and long-term exposure to environmental agents (e.g., aflatoxin). The exact pathogenesis is unclear. With HBV and HCV, both of which become integrated into the host DNA, repeated cycles of cell death and regeneration afford the potential for development of cancer-producing mutations. Aflatoxin, produced by food spoilage molds (e.g., *Aspergillus flavus* and *Aspergillus parasiticus*), is a known human carcinogen and is endemic in certain areas. A particularly susceptible site for aflatoxin mutation is the *TP53* tumor suppressor gene [125].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Association for the Study of Liver Diseases recommends that patients at high risk of developing hepatocellular carcinoma be entered into surveillance programs, provided they would be candidates for hepatocellular carcinoma treatment.

(https://journals.lww.com/hep/fulltext/2023/12000/aasld_practice_guidance_on_prevention,_diagnosis,.27.aspx. Last accessed August 12, 2024.)

Level of Evidence/Strength of Recommendation: Level 2/Strong

Clinical Manifestations and Diagnosis

What are the usual initial signs and symptoms of hepatocellular cancer?

The manifestations of HCC often are insidious in onset and masked by those related to cirrhosis or chronic hepatitis. The initial signs and symptoms include weakness, anorexia, weight loss, fatigue abdominal swelling, a sensation of abdominal fullness, and a dull, aching abdominal pain. Ascites, which can obscure weight loss, is common. Jaundice, if present, usually is mild. There may be a rapid increase in liver size and worsening of ascites in people with pre-existing cirrhosis. Usually, the liver is enlarged when these symptoms appear. Various paraneoplastic syndromes (disturbances due to ectopic hormone or growth factor productions by the tumor) have been associated with hepatocellular cancer, including erythrocytosis, hypoglycemia, and hypercalcemia. Serum α-fetoprotein is present during fetal life but barely detectable in the serum after 2 years of age. When high levels of α-fetoprotein are found in adults, it is usually indicative of hepatocellular carcinoma, although not all primary liver cancers produce α-fetoprotein.

Additional imaging, such as ultrasonography, computed tomography (CT) scan, and magnetic resonance imaging (MRI), are recommended for diagnosis. Liver biopsy may be used to confirm the diagnosis [131; 132; 133; 134]. Genetic testing can reveal susceptibility.

Treatment

There is no agreement on a single treatment strategy for patients with HCC. Selection of treatment is complex due to several factors, including [135]:

- Underlying liver function
- Extent and location of the tumor
- General condition of the patient

Several treatments for HCC are associated with long-term survival, including surgical resection, liver transplant, and ablation. There are no large, robust, randomized studies that compare treatments considered effective for early-stage disease, nor are there studies comparing these treatments with best supportive care. Often, patients with HCC are evaluated by a multidisciplinary team that includes hepatologists, radiologists, interventional radiologists, radiation oncologists, transplant surgeons, surgical oncologists, pathologists, and medical oncologists.

Best survival rates are achieved when the HCC can be removed either by surgical resection or liver transplant. Surgical resection is usually performed in patients with localized HCC and enough functional hepatic reserve. For patients with decompensated cirrhosis and a solitary lesion (<5 cm) or early multifocal disease (up to three lesions, ≤3 cm in diameter), the best option is liver transplant, but the limited availability of liver donors restricts the use of this approach.

Transarterial chemoembolization, multikinase inhibitors, and immunotherapy are noncurative treatments for HCC that improve survival. For patients with recurrent disease with metasteses and/or vascular involvement, palliative therapy is the most appropriate approach [135].

Cholangiocarcinoma

Cholangiocarcinoma, with an incidence of 1.6 per 100,000 in North America, occurs much less frequently than hepatocellular carcinoma [136]. The etiology, clinical features, and prognosis vary considerably with the part of the biliary tree that is the site of origin. Distal and perihilar bile duct cancers frequently cause biliary tract obstruction, leading to the following symptoms [137]:

- Jaundice
- Weight loss
- Abdominal pain
- Fever
- Pruritus

Intrahepatic bile duct cancer may be relatively indolent and difficult to differentiate clinically from metastatic adenocarcinoma deposits in the liver.

Cholangiocarcinoma is not associated with the same risk factors as hepatocellular carcinoma. Instead, most of the risk factors revolve around long-standing inflammation and injury of the bile duct epithelium. Bile duct cancer may occur more frequently in patients with a history of primary sclerosing cholangitis, chronic ulcerative colitis, choledochal cysts, or infections with the liver fluke *Clonorchis sinensis* [137].

Treatment

The treatment of bile duct cancer depends primarily on whether the cancer can be completely removed by surgery. Localized intrahepatic and extrahepatic bile duct cancer may be completely resected. However, these tumors represent a very small number of cases that are usually in the distal common bile duct. Among patients treated with surgical resection, long-term prognosis varies depending on primary tumor extent, margin status, lymph node involvement, and additional pathological features [137].

Extended resections of hepatic duct bifurcation tumors (also known as Klatskin or hilar tumors) to include adjacent liver, either by lobectomy or removal of portions of segments 4 and 5 of the liver, may be performed. If major hepatic resection is necessary to achieve a complete resection, postoperative hepatic reserve should be evaluated [137].

Unfortunately, most cases of intrahepatic, distal, and perihilar bile duct cancer are unresectable and cannot be completely removed. Often, the cancer invades directly into the portal vein, the adjacent liver, along the common bile duct, and to adjacent lymph nodes. Portal hypertension may result from invasion of the portal vein. Spread to distant parts of the body is uncommon, but intra-abdominal metastases, particularly peritoneal metastases, do occur. Transperitoneal and hematogenous hepatic metastases also occur with bile duct cancer of all sites. Moreover, most patients who undergo resection will develop recurrent disease within the hepatobiliary system or, less frequently, at distant sites.

In locally advanced disease, trials have evaluated chemoradiotherapy with the goal of improved local control and potential downstaging for surgical resection [137]. These approaches have not been compared with standard therapy, and the curative potential is unknown. For patients with unresectable bile duct cancer, management is directed at palliation.

Metastatic Tumors

Metastatic tumors of the liver are much more common than primary tumors. Common sources include colorectal cancer and those spread from breast, colon, lung, or urogenital cancer. In addition, tumors of neuroendocrine origin can spread to the liver. It often is difficult to distinguish primary from metastatic tumors with the use of CT scans, MRI, or ultrasonography. The diagnosis may be confirmed by biopsy [132; 133].

CANCER OF THE GALLBLADDER

Cancer of the gallbladder is rare. In 2024, there will be an estimated 12,350 new cases diagnosed and 4,530 deaths [138]. Malignant tumors are usually columnar cell carcinomas that cause symptoms of inflammation and obstruction. In part because of its rarity, biliary carcinoma may be overlooked or confused with cholelithiasis [139; 140]. The most common symptoms caused by gallbladder cancer are jaundice, pain, and fever.

Treatment

Patients with stage I disease have cancer confined to the gallbladder wall that can be completely resected. Patients with stage I tumors that are discovered incidentally and resected during routine cholecystectomy have five-year survival rates of nearly 100% [138]. Previously unsuspected gallbladder cancer that is incidentally discovered in the mucosa of the gallbladder during pathological examination is curable in more than 80% of patients. However, symptomatic gallbladder cancer that is suspected prior to surgery often penetrates the muscularis and serosa. This type of gallbladder cancer is curable in less than 5% of patients [138].

Treatment options for localized and locally advanced gallbladder cancer include [138]:

- Surgery
- External-beam radiation therapy (EBRT)
- Clinical trials exploring the use of radiation therapy and radiosensitizer drugs to improve local control

During laparoscopic removal of an unsuspected cancer, implantation of carcinoma at all port sites (including the camera site) is possible. All port sites are typically excised completely, even for stage I cancers.

Patients with T2 (tumor invades the perimuscular connective tissue on the peritoneal or hepatic side) or T3 (tumor perforates the serosa and/or directly invades the liver and/or one other adjacent organ or structure) disease have higher rates of unsuspected invasive disease at the time of diagnosis [138]. Eligible patients may undergo re-exploration to resect liver tissue near the gallbladder bed, portal lymph nodes, and lymphatic tissue in the hepatoduodenal ligament. Retrospective analyses suggest that extended re-resection can delay recurrences and potentially improve survival [138].

For patients with locoregional lymph node involvement (at the cystic duct, common bile duct, hepatic artery, and portal vein), long-term disease-free survival can occasionally be achieved with radical resection. In patients with jaundice, preoperative percutaneous transhepatic biliary drainage for relief of biliary obstruction should be considered [138].

Surgery with curative intent is not considered possible in patients with metastatic spread beyond the locoregional lymph nodes or to distant organs [138].

The use of EBRT with or without chemotherapy as a primary treatment has been reported to produce short-term disease control in small groups of patients. Similar benefits have been reported for radiation therapy, with or without chemotherapy, administered after resection [138]. However, there is limited evidence supporting the use of adjuvant radiation therapy, even for patients with high-risk localized disease [138].

CHOLEOLITHIASIS

Cholelithiasis, the formation of gallstones, can lead to obstruction of the bile ducts associated with obstructive icterus and severe, colicky pain. An estimated 20 million Americans have cholelithiasis, and almost 1 million new cases are diagnosed each year [129; 139; 140; 141].

Several predisposing factors are related to development of cholelithiasis [129; 139; 140; 141]. Women are affected four times as frequently as men, and taking oral contraceptives are twice as like likely as other women to develop gallstones. Further, multigravidas women are more likely to develop the condition than those who have not been pregnant. Persons older than 40 years of age are affected more often than younger persons. High fat intake and cholesterol saturation of bile are considered predisposing factors, and obesity and diabetes are associated with increased risk of gallstone formation. Persons who have had extensive bowel resections (as for Crohn disease) have a threefold to fivefold higher incidence of cholelithiasis, possibly because recirculation of bile salts is interrupted.

Cholesterol saturating of bile appears to be a major factor in development of gallstones. The underlying cause may be dysfunction of the hepatic cells where bile is synthesized. Bile salts precipitate from supersaturated bile, forming nuclei for accretion of layers of cholesterol, calcium, and bilirubin to form calculi within the gallbladder.

Gallstones are classified as either cholesterol or pigment stones. Cholesterol stones are usually of mixed composition and contain more than 70% cholesterol plus calcium salts, bile pigments, fatty acids, and proteins. There is a high incidence of cholesterol stones in North America. Pigment stones are primarily calcium and bilirubin and contain less than 10% cholesterol. Pigment stones are less common in North America but have a high prevalence in Japan [139; 140; 141; 142].

Clinical Manifestations

Calculi formed in the gallbladder may move into the cystic duct, the common bile duct, or even into the liver via the hepatic ducts. Calculus obstruction of the pancreatic duct may cause pancreatitis [141; 143].

The most common symptom of cholelithiasis is colicky pain believed to be related to spasms of the sphincter of Oddi. Pain may also be related to obstruction and distention of a bile duct. Usually, the pain is felt in the epigastrium or the right upper quadrants of the abdomen, but it may radiate up the back between the scapulae to the right shoulder or around the abdomen to the back, making it difficult for the patient to assume a comfortable position. Some patients will report laying in the supine position often worsens the discomfort. Biliary colic may occur at varying intervals following meals or may wake the patient from sleep. Usually, symptoms occur at progressively shorter intervals after ingestion of almost any food. Occasionally, however, a single pain episode will never be repeated [129; 139; 140; 141].

In addition to the characteristic pain, nausea and vomiting are common, as is elevated temperature. Distention of the bile ducts stimulates the vomiting center. If the common bile duct is obstructed by a calculus, greenish-yellow jaundice develops. Pruritus often develops before the jaundice is visible in the sclera. Icterus is accompanied by pale stools and dark, frothy urine. Ecchymoses may be evident [139; 140; 141].

Laboratory and diagnostic studies assist in confirming the diagnosis. White blood cell levels, direct bilirubin levels, prothrombin time, alkaline phosphatase, and serum lipid levels will be elevated. Urine urobilinogen levels will decrease, but bilirubin will be found in the urine. Abdominal ultrasound and increased alkaline phosphatase (ALP) levels can help establish a diagnosis of cholelithiasis. Cholecystography, cholangiography, or endoscopic retrograde cholangiopancreatography (ERCP) may be required [139; 140; 141].

Therapeutic Measures

If symptoms are mild, a low-fat diet may be sufficient to control them. The diet would be high in proteins and carbohydrates [144]. Depending on the patient's nutritional status, intravenous glucose and protein supplementation may be indicated. A nutritious diet promotes healing and helps prevent hepatic damage. Vitamin K may be required if coagulation abnormalities are demonstrated [145].

For acute attacks, treatment often includes medications such as butylscopolamine, flopropione, and nonsteroidal anti-inflammatory drugs (NSAIDs). For patients at risk for the development or exacerbation of cholelithiasis, oral ursodeoxycholic acid (UDCA) is recommended for prophylaxis [146].

There are a variety of options for minimally invasive management. Extracorporeal shock wave lithotripsy (ESWL) and oral chemical dissolution therapy were previously used, but both have largely been replaced in recent years. . Both techniques are rarely used in clinical practice in recent years.

Today, many patients with recurrent and/or severe disease undergo ERCP with or without stent placement. If surgical Management is indicated, the preferred approach is laparoscopic cholecystectomy [146].

Specific Nursing Measures

In addition to comfort measures and administering analgesics and other prescribed medications, nurses can consult with the dietitian and the patient to work out a palatable low-fat diet. The patient may find a list of preferred, appropriate foods useful [59].

LIVER TRANSPLANTATION

What is the usual duration of liver transplantation surgery?

Liver transplantation, one of the most common types of solid organ transplant, is the replacement of the diseased liver by an allograft from a brain-dead donor or a partial replacement of the liver by a living related donor. Dr. T.E. Starzl and associates at the University of Colorado pioneered this treatment modality in the early 1960s. By the end of the decade, surgeons in Pennsylvania and England were performing the procedure. By the beginning of the 21st century, liver transplantation had been performed at dozens of medical centers in the United States, Canada, and Western Europe. Although survival rates in the early programs were only 30%, improvements in technique and timing of the transplant have now brought the one-year survival rate to approximately 90% and the five-year survival rate to approximately 75% [147].

Children and adults who have irreversible liver disease or defects that cannot be overcome or managed by medical options are candidates for liver transplants. In children, the most common reasons for liver transplantation include biliary atresia, neonatal hepatitis, congenital hepatic fibrosis, alpha 1-antitrypsin deficiency, and disorders of metabolism that result in inappropriate storage within the liver or significant liver damage from the buildup of metabolites. The most common diseases necessitating liver transplantation in adults are chronic viral hepatitis (HCV in the United States, HBV in Europe), biliary cirrhosis, alcoholic cirrhosis, sclerosing cholangitis, cryptogenic cirrhosis, Caroli disease, primary hepatocellular malignancies, hepatic adenomas, and hepatic vein thrombosis [148; 149]. Biliary atresia remains a common indication for liver transplantation in pediatric patients [150].

The Model for End-Stage Liver Disease (MELD) is a prognostic system that is now widely accepted as a tool for predicting survival of patients with cirrhosis. MELD, in conjunction with international normalized ratio, serum creatinine, serum bilirubin, and sodium, has been evaluated as a prognostic indicator for cirrhosis regardless of cause. Transplant centers utilize the MELD score in prioritizing clients for transplant [147; 151]. The Pediatric End-Stage Liver Disease (PELD) is used for children younger than 12 years of age [147].

Though patients may have a disease process that is an indication for liver transplant, the presence of compounding factors may provide a contraindication for the therapy. At one time, HIV disease was considered a contraindication for liver transplant. While patients with advanced HIV disease are not transplant candidates, HIV disease that is in an early stage or is controlled by antiretroviral therapy is no longer a contraindication for transplantation therapy. Similarly, persons older than 60 years of age were at one time excluded from this therapy, but persons older than 60 years of age who are healthy other than their liver disease can now be considered for candidacy. Active drug or alcohol use, metastatic cancer, uncontrolled bacterial or fungal infections, advanced cardiac or lung disease, and uncorrectable life-threatening congenital anomalies remain contraindications for liver transplantation.

Relative contraindications for liver transplantation are those factors that in isolation would not preclude a patient from receiving a transplant but in combination might decrease the probability that the patient would be approved. Examples of relative contraindications include chronic HBV with rapidly replicating virus, significant psychiatric disorder that may interfere with the patient's ability to follow the post-transplant regimen, significant renal disease not associated with the hepatic disease, and previous hepatic or biliary surgery [149].

Historically, donor organs have been obtained from cadavers. In 1998, the use of living related donors became an option in certain cases [152; 153]. Partial liver transplantation from living related donors results in a 20% morbidity rate for the donor. Therefore, cadaveric transplant remains the procedure of choice. The following discussion addresses only cadaveric transplants.

In 2020, the Organ Procurement and Transplantation Network implemented a new liver distribution system called the acuity circle policy, which emphasizes the medical urgency of liver transplant candidates and the distance between the donor and transplant hospitals. The new system replaces the use of decades-old geographic boundaries of 58 donation service areas and 11 transplant regions [154]. Under the new policy, livers from all deceased donors will first be offered to the most urgent liver transplant candidates listed at transplant hospitals within a radius of 500 nautical miles of the donor hospital. Following offers to the most urgent candidates, livers from adult donors will be offered to candidates at hospitals within distances of 150, 250, and 500 nautical miles of the donor hospital. These offers are grouped by medical urgency [147].

Donor livers are usually obtained from brain-dead persons younger than 60 years of age who are free from bloodborne pathogen infections (HCV, HBV, HIV), are not septic, have no existing liver disease, and have not recently experienced abdominal trauma. Some centers consider the use of livers from HBV- or HCV-infected donors for recipients infected with the same strain or subspecies of virus [155]. When donor livers are infected but not yet showing signs of cirrhosis, preliminary results indicate that recipient outcomes are not significantly different from those receiving uninfected livers.

Donor and recipient should have compatible body size and A, B, O blood groups. Unlike kidney transplants, however, donor and recipient do not have to have matching tissue types. The liver is viable for up to 20 hours after removal from the donor, but most centers prefer for the transplant surgery to be completed within 12 hours after organ harvest.

Liver transplantation surgery typically requires a procedure of 6 to 12 hours in duration; in more complex circumstances, the surgery has lasted up to 18 hours. During the procedure, the patient is at risk for coagulopathies, electrolyte disturbances, hypoglycemia, and a large volume of blood loss.

Various combinations of immunosuppressive drugs (monoclonal and polyclonal antibodies) have been used to reduce the probability of post-transplant rejection. It is desirable to try to prevent or minimize the adverse effects of these drugs, including infections, malignancy, and general drug toxicity. In the immediate post-transplant period, a common drug regimen includes a combination of a monoclonal antibody, mycophenolate mofetil, corticosteroids, and a calcineurin inhibitor such as cyclosporine or tacrolimus [148]. According to Hanto, the addition of an anti-IL-2 receptor monoclonal antibody (basiliximab or daclizumab) can result in a decrease in rejection rate from 43.5% to 35.1% [156]. Sirolimus is a newer drug that appears to be useful, especially in patients with renal insufficiency.

Chronic suppressive therapy is usually accomplished with tacrolimus and mycophenolate mofetil. Steroids are weaned within a few weeks of transplantation, except in the presence of autoimmune hepatitis. Liver transplant recipients require lower doses of immunosuppressive therapy than patients receiving other solid organ transplants. Nevertheless, providers should be attentive to drug-drug interactions and therapeutic monitoring of these medications [157].

The process of rejection is insidious in the majority of liver transplantation cases; hyperacute rejection rarely occurs. Most episodes of acute rejection occur within the first six months after the transplant (usually between three and six months) but can be reversed with steroids. In approximately 10% to 20% of patients, steroid resistance occurs, requiring treatment with a monoclonal antibody, such as muromonab-CD3, or a polyclonal antibody, such as thymoglobulin [156]. Acute rejection episodes seldom threaten graft survival. Patient survival rates are 84% with living-donor grafts and 83% with deceased-donor grafts at one year and 34% with living-donor grafts and 46% with deceased-donor grafts at five years [157].

CONCLUSION

With knowledge of hepatic and biliary structure and function and the dynamic pathology that intrudes and impedes normal function, nurses are better able to provide quality and often life-saving actions. An awareness of why symptoms appear leads to quicker reporting of changes in the patient's condition. Nurses should also be prepared to perform immediate interventions based on standing orders and the recognition of what needs to be done in order to provide safe, quality care. This knowledge changes what could be only technical care to professional care through use of decision making skills built upon the knowledge of pathophysiology.

CASE STUDIES

CASE ONE: ESOPHAGEAL VARICES

Present Illness

Patient A is a man, 60 years of age, who is admitted to the hospital for treatment of acute gastrointestinal bleeding. The patient had a similar episode five weeks ago. An upper endoscopic exam at that time revealed a bleeding esophageal varix for which he received band ligation therapy. He is well-known to the medical community for chronic alcohol use. He has lost several jobs for drinking in the workplace or showing up for work drunk. He has lost his driver's license for drunk driving, and his drinking has placed a significant strain on his marriage. He and his wife are currently separated. He has tried several self-help programs to stop drinking as well as Alcoholics Anonymous, all with little success.

Medical History

Patient A has been hospitalized five times during the previous 30 months. Most recently, he was discharged five weeks ago following treatment for bleeding esophageal varices. He has a 44-year history of cigarette smoking (one pack per day), was diagnosed five years ago with alcoholic cirrhosis, and currently drinks an unknown amount of liquor daily. He previously reported drinking 6 to 12 beers per day for many years.

On previous admissions, Patient A has been treated for acute pancreatitis twice, alcohol withdrawal seizures, delirium tremens, ascites, coagulopathy, esophageal varices, peptic ulcer disease, anemia, and gastritis, all of which were determined to be related to his alcohol use. Medications at last discharge included:

- Lactulose (30 mL four times per day)
- Spironolactone (100 mg per day)
- Furosemide (80 mg per day)
- Propranolol (30 mg per day)
- Famotidine (40 mg twice per day)

Assessment and Diagnosis

Patient A was found unconscious and face down in a pool of bright red, bloody vomitus by his neighbor. He is resuscitated and taken to the hospital by ambulance and is admitted to the intensive care unit (ICU). Upon admittance to the ICU, a full physical exam is conducted (***Table 1***) and laboratory blood testing is ordered (***Table 2***). Intravenous infusion with a solution of D5W and colloid is started through a central line. Oxygen is started at 3 L/min. Octreotide is administered to help stop the bleeding. An echocardiogram is conducted.

Based on the results of the assessment, Patient A is diagnosed with acute alcohol-related pancreatitis.

Study Questions

1. *Explain the pathophysiology of each of the following clinical manifestations in this patient.*
   a. *Spider angiomas*
   b. *Splenomegaly*
   c. *Edema*
   d. *Jaundice and icteric sclera*
2. *Why has the primary care provider noted the absence of asterixis?*
3. *What is the significance of the renal test results?*
4. *What is the significance of the liver enzyme test results?*
5. *What are the pathophysiology and significance of the total and indirect bilirubin test results?*
6. *Is blood clotting a concern at this time in this patient?*
7. *Why might hemoglobin concentration and hematocrit be abnormal?*
8. *Does this patient have an arterial blood gas problem?*
9. *Give a reasonable explanation for the pathophysiology of the patient's blood glucose concentration.*
10. *What evidence is provided that this episode is not associated with another attack of alcohol-induced acute pancreatitis?*
11. *What is the purpose of prescribing lactulose for patients with chronic liver disease?*
12. *Why are diuretics appropriate for patients with chronic hepatic disease?*

PATIENT A'S PHYSICAL EXAM RESULTS	
Parameter	**Findings**
General appearance	Thin, unkempt White man Height: 5 feet 10 inches (177.8 cm) Weight: 151 pounds (68.5 kg)
Skin	Markedly jaundiced Spider angiomas evident on arms Normal turgor No palmar erythema
Head and eyes	Icteric sclera Pupils are equal, round, and reactive to light and accommodation Extra-ocular motion intact Oropharynx dry, with no erythema or lesions present
Ears	Tympanic membranes intact
Neck	Supple with no nodules Negative for jugular vein distention, thyromegaly, and lymphadenopathy
Chest	Good air exchange bilaterally
Abdomen	Soft, with mild distension and hyperactive bowel sounds Splenomegaly Negative for guarding or rebound tenderness
Extremities	Warm with mild (1+) edema Pulses symmetric at 2+ Muscle tone normal Full range of motion throughout
Genitourinary system	Normal male Stool positive for heme
Neurologic status	Alert and oriented Slow to answer questions Cranial nerves II–XII intact Deep tendon reflexes brisk and equal bilaterally
Cardiovascular system	Tachycardia with normal rhythm Normal S1 and S2 with no additional heart sounds No murmurs or rubs heard Normal sinus rhythm
Vital Signs	
Blood pressure	90/60 mm Hg
Temperature	98.0° F
Heart rate	112 bpm with regular irregular rhythm
Respiratory rate	14 breaths per minute
Source: Author	*Table 1*

CASE STUDY TWO: CIRRHOSIS

Present Illness

Patient B is a woman, 48 years of age, who presents to the emergency department complaining of a four-week history of progressive abdominal swelling and discomfort. She has no other gastrointestinal symptoms and has a normal appetite and normal bowel habits. Her past medical history is significant only for three pregnancies, one of which was complicated by hemorrhage, requiring a blood transfusion. She has been married for 20 years, exercises, does not smoke, and drinks only occasionally. On pointed questioning, she admits that she was "wild' in her youth and did use cocaine once or twice at parties many years ago. She does not currently use illicit drugs. She tested HIV-negative at the time of the birth of her last child.

PATIENT A LABORATORY BLOOD TEST RESULTS	
Test	**Result**
Blood type	B+
Sodium	135 meq/L
Potassium	4.6 meq/L
Chloride	103 meq/L
Bicarbonate	22 meq/L
Blood urea nitrogen (BUN)	10 mg/dL
Creatinine	1.1 mg/dL
Fasting blood glucose	140 mg/dL
Hemoglobin	9.4 g/dL
International normalized ratio (INR)	2.3
Hematocrit	28%
White blood cell count	10,000/mm^3
Platelets	160,000/mm^3
Total bilirubin	10.4 mg/dL
Indirect bilirubin	9.9 mg/dL
Amylase	43 IU/L
PaO_2	85 mm Hg
$PaCO_2$	245 mm Hg
pH	7.38
NH_3	59 mcg/dL
Prothrombin time (PT)	23 seconds
Partial thromboplastin time (PTT)	54 seconds
Aspartate transaminase (AST)	119 IU/L
Alanine transaminase (ALT)	94 IU/L
Total protein	4.9 g/dL
Albumin	2.9 g/dL
Calcium	8.9 mg/dL
Phosphorus	2.8 mg/dL
HIV RNA	Negative
Source: Author	*Table 2*

On examination, her temperature is 100.3 degrees F, her heart rate is 88 bpm, and her blood pressure is 94/60 mm Hg. She is thin, her complexion is sallow, her sclerae are icteric, her chest is clear, and her heart is regular with no murmur. Her abdomen is distended and with mild diffuse tenderness, hypoactive bowel sounds, shifting dullness to percussion, and a fluid wave. She has no peripheral edema. Laboratory studies are normal except for the following:

- Sodium: 120 mEq/L
- Albumin: 2.8 mg/dL
- Total bilirubin: 4 mg/dL
- Prothrombin time: 15 seconds
- Hemoglobin: 12 g/dL, with a mean cell volume (MCV) of 102 fL
- Platelet count: 78,000/mm^3

Patient B is diagnosed with ascites caused by portal hypertension as a complication of hepatic cirrhosis. Paracentesis is performed to evaluate the ascitic fluid to try to determine its likely etiology, as well as evaluate for the complication of spontaneous bacterial peritonitis.

CASE STUDY THREE: JAUNDICE

Present Illness

Patient C is a Black man, 33 years of age, who presents to the office for an acute visit with nausea and diarrhea that he has had for the past week. Along with these symptoms, he has had a low-grade fever, some right upper quadrant abdominal pain, and has noticed that his eyes seem yellow.

Medical History

Patient C has no significant medical history and takes no medications regularly. He denies alcohol, tobacco, or IV drug use. He works as a pastor in a local church that went on a mission to build a medical clinic in a rural area of Central America about five weeks ago. While there, he had a mild case of diarrhea, but otherwise has felt well.

Assessment and Diagnosis

On examination, Patient C is a well-developed man who appears to be moderately ill. His temperature is 99.8°F, his blood pressure is 110/80 mm Hg, his pulse is 90 beats/minute, and his respiratory rate is 14 breaths/minute. He has a prominent yellow color to his eyes and under his tongue. His mucous membranes are moist. Lung and cardiac examinations are normal. His abdomen has normal bowel sounds and tenderness in the right upper quadrant. His liver edge is palpable just below the costal margin. There are no other masses felt, no rebound, and no guarding. On rectal examination, he has clay-colored soft stool that is hemoccult negative.

Based on the examination and history, Patient C is diagnosed with jaundice, likely related to acute hepatitis A infection. Anti-hepatitis A IgM testing confirms infection. The most probable source of infection is ingestion of contaminated food or water while on his mission.

For this patient, treatment focuses on supportive care and palliation of symptoms. The infection is also reported to the local health department. Close household or sexual contacts are provided with hepatitis A prophylaxis.

CASE STUDY FOUR: CHRONIC HEPATITIS C

Patient D is a paramedic, 48 years of age. Laboratory work obtained during his annual physical examination reveals hyperlipidemia; complete blood count, glucose, blood urea nitrogen (BUN), and electrolytes are within normal range. With the exception of his weight (15 pounds heavier than indicated for his height), his exam identifies no abnormalities. After two months of a diet and exercise program, his cholesterol level is 256. Therefore, his physician elects to begin a lipid-lowering agent. A baseline liver profile is drawn prior to initiation of the medication. Because the patient is in a profession that is high-risk for bloodborne pathogen exposure, an HCV antibody test with reflex to qualitative HCV RNA is ordered. The liver profile reveals an AST of 226 Units/L and an ALT of 282 Units/L. HCV antibody and reflex quantitative HCV RNA are both positive.

The physician reviews Patient D's history and medications. He has been a paramedic for 25 years. He was immunized against HBV in 1999. During his career, he has experienced several exposures to blood (usually blood splashes, but also two needlesticks from IV needles). His most recent exposure was two years ago. An HIV test six months post-exposure was negative. He does not recall hepatitis testing being performed at that time.

Patient D's surgical history includes a hernia repair in childhood and removal of skin lesions three times in the past eight years. He has had no transfusions. He is the widowed father of two teenage children. His wife died six years ago from ovarian cancer.

The patient has never smoked. He drinks about six beers per week and rarely drinks hard liquor. He denies any history of illicit drug use. Although the patient has no current prescription medications, he uses several herbal preparations including garlic, ginkgo, and an antioxidant preparation. The patient takes ibuprofen for pain, consuming 6 to 10 tablets (200 mg each) per month.

Although alcohol consumption and herbal antioxidants can both cause liver inflammation, the degree of his liver inflammation is much higher than would be expected from limited use of these two factors. The patient is diagnosed with chronic HCV infection.

In order to evaluate the extent of liver damage and determine an appropriate treatment plan, the physician orders an HCV RNA quantitative PCR and genotype as well as a repeat hepatic panel, platelet count, and PT. Shear wave elastography is also ordered. The laboratory results are:

- Platelets: 237 × 10^9/L
- ALT: 253 Units/L
- AST: 214 Units/L
- PT INR: 1.0
- HCV RNA: 350,000 IU/L
- HCV genotype: 3

Based upon these laboratory results, the calculated Fib-4 score is 2.72. The elastography reflects a fibrosis score of F1. No masses are identified on ultrasound. Because the genotype of the virus is 3, resistance testing is ordered. Substitution mutation *Y93H* is not present.

Treatment options appropriate for HCV genotype 3, and the timing of therapy in relation to his degree of fibrosis and anticipated progression of disease are discussed with Patient D. He is advised to eat a nutritious, balanced diet and abstain completely from alcohol. Although he is not currently sexually active, the patient is educated about the low but present risk of sexual transmission of HCV and how to minimize the risk of transmission. A test for HAV antibody is found to be negative. Immunization against HAV is also recommended, as acquiring an acute case of HAV in a patient with pre-existing chronic hepatitis can be much more serious that either condition alone. He is also provided pneumococcal immunization, as persons with chronic liver disease are at increased risk of pneumococcal infection and complications. Because of uncertainty as to how recently he acquired the infection, the decision is made to defer treatment for three to four months while monitoring the course of the infection.

Four months after the initial diagnosis, there has been no improvement in Patient D's liver function tests: the ALT is 318 Units/L and AST is 287 Units/L. The HCV RNA remains detectable in the blood, and the viral load has increased to 450,000 phages/cc. He is advised to begin antiviral treatment; therapeutic options are discussed in relation to efficacy, potential drug interactions, and cost reimbursement priorities, bearing in mind that he is a treatment-naïve patient with no evidence of cirrhosis. The recommended course of therapy is the 12-week, two-drug oral regimen of sofosbuvir (400 mg) and velpatasvir (100 mg) for a duration of 12 weeks (reported SVR rate: 95% in clinical trials for genotype 3).

On treatment, the patient experiences transient nausea and persistent mild fatigue, but is compliant with the recommended duration of therapy. At 12 weeks, the ALT and AST are both within normal range and HCV RNA is undetectable. Patient D is asked to return in three months to continue his hyperlipidemia treatment follow-up.

CASE STUDY FIVE: PANCREATITIS-GALLSTONE-INDUCED

Present Illness

Patient E is a Hispanic woman, 42 years of age, who presents to the emergency department complaining of 24 hours of severe, steady epigastric abdominal pain, radiating to her back, with several episodes of nausea and vomiting;. She has had similar painful episodes in the past, usually in the evening following heavy meals, but they always resolved spontaneously within an hour or two. This time, the pain has not improved, so she is seeking medical attention.

Medical History

Patient E has no prior medical history and takes no medications. She is married, has three children, and does not drink alcohol or smoke cigarettes.

Assessment and Diagnosis

On examination, Patient E is afebrile. She is experiencing tachycardia, with a heart rate of 104 beats per minute. Her blood pressure is 115/17 mm Hg, and she has shallow respirations of 22 breaths per minute. She is moving uncomfortably on the stretcher, her skin is warm and diaphoretic, and she has scleral icterus. Her abdomen is soft and mildly distended, with marked right upper quadrant and epigastric tenderness to palpation, hypoactive bowel sounds, and no masses or organomegaly appreciated. Her stool is negative for occult blood. Laboratory studies are significant for:

- Total bilirubin: 9.2 g/dL, with a direct fraction of 4.8 g/dL
- Alkaline phosphatase: 285 IU/L
- Aspartate aminotransferase (AST): 78 IU/L
- Alanine aminotransferase (ALT): 92 IU/L
- Amylase: 1,249 IU/L (elevated)
- Leukocyte count: 16,500/mm^3, with 82% polymorphnuclear cells and 16% lymphocytes

Right upper quadrant abdominal ultrasonography shows a distended gallbladder, with several stones.

Based on the assessment, Patient E is diagnosed with acute pancreatitis resulting from choledocolithiasis. The patient is started on systemic antibiotics and prepared for removal of the stones.

CASE STUDY SIX: HIV AND CHRONIC HBV COINFECTION

Patient C is a man, 32 years of age, with a history of injection drug use, who participated in a free HIV testing day. His screening test was found to be positive. A confirmatory test conducted at the health department was also positive. He has therefore been referred to the Infectious Disease Clinic of a large university medical center for follow up.

During his first visit, the patient indicates that he injected drugs off and on beginning at 19 years of age. His first two experiences with rehabilitation failed, but he has been "clean" for two years, since his best friend died of an overdose. He reports that he also snorted cocaine occasionally during the years he used injected drugs.

The patient's medical history includes a hospitalization for a motorcycle accident at age 24, with surgery on his right leg both on that admission and again about a year later. He received 2 units of blood during the first admission. The patient denies a history of heart disease, neurologic disorders, or endocrine disorders. He has had pneumonia both in adolescence and again last year.

The patient's parents are living and in good health. Grandparents all have hypertension, and maternal grandmother has type 2 diabetes. The patient smokes 1/2 to 1 pack of cigarettes per day and consumes two or three drinks per day. The patient's current medications include acetaminophen or ibuprofen as needed for leg pain and paroxetine for anxiety and depression.

Physical examination reveals no acute distress. Vital signs are within normal limits, and sclerae are non-icteric. Oral cavity is free from thrush and leukoplakia. Cervical lymph nodes are palpable but moveable and nontender. Heart sounds are normal; lungs are clear. Abdomen is soft; both liver and spleen are palpable. Neurologic exam is normal. The patient has full function in upper extremities and left leg; right leg has a slight decrease in strength and a moderate decrease in range of motion.

Initial laboratory tests ordered by the nurse practitioner (NP) include an HIV PCR viral load, a CD4 count, a CBC, a chemistry panel, and a liver profile. Because of the high incidence of HCV and/or HBV coinfection in persons whose HIV was acquired percutaneously, the NP also orders a hepatitis profile. Baseline tuberculosis testing is also recommended for persons with HIV who are entering care. Therefore, a T-SPOT interferon gamma release assay is also ordered. The patient is instructed to return in 72 hours to review lab results and formulate a treatment plan.

Upon his return, all results except the HIV PCR are available. His CD4 count is 246. Hematocrit is 44%, hemoglobin 15 gm/dL, and WBC is 3,800. The liver profile reveals an alkaline phosphatase of 143 Units/mL, AST 358 Units/L, ALT 383 Units/L, total bilirubin 1.2 mg/dL, and albumin 2.8 gm/dL. The remainder of the chemistry panel is unremarkable. Hepatitis profile is positive for HBsAg, HBeAg, and total anti-HBc. The anti-HAV, anti-HCV and anti-HBc IgM are negative. The T-SPOT TB test is negative.

The NP informs Patient C that he is coinfected with HIV and HBV and instructs him about the problems associated with HIV/HBV coinfection. He is given HAV and pneumococcal immunizations and options for antiretroviral therapy are discussed. Because of its effectiveness against both HIV and HBV, a medication regimen including tenofovir with lamivudine or tenofovir with emtricitabine should be utilized. A third medication for HIV viral suppression should be added, with consideration of the hepatotoxicity profile of the medication. After discussing available options with limited hepatotoxicity, an integrase inhibitor is selected as the third active agent in the combination. A single tablet medication containing bictegravir, emtricitabine, and tenofovir alafenamide in a once daily formulation was therefore selected to treat both HIV and HBV.

Information is provided to Patient C regarding safe sex practices. He is also instructed to abstain from alcohol and to use ibuprofen (or no more than 2 g acetaminophen in 24 hours) for pain control. The NP also orders a PT to be drawn; in addition, the patient is referred to hepatology for a liver biopsy to be performed in order to evaluate the progression of the liver disease. The patient is scheduled for a follow-up visit in four weeks, with a repeat HIV PCR performed at that time. In the interim, his baseline HIV PCR is found to be 123,000.

Upon his return to the office, Patient C is advised that the liver biopsy revealed periportal inflammation with focal necrosis and bridging fibrosis. PT is 15.6 seconds (control: 12 seconds). These findings indicate severe, advanced liver disease and the guarded prognosis. Because of the severity of his liver disease, he is not a good candidate for PegIFN therapy. The patient's current HIV status precludes his being a transplant candidate at the time. The recommended treatment plan for Patient C is to maximize his HIV suppression while minimizing his continued liver damage. If he is compliant with his therapy, he should be able to maintain a fairly good quality of life and postpone liver failure for three years or more. Prolonging the time until liver failure also provides the opportunity to improve immunocompetency. Some liver transplant centers now accept HIV-positive patients, provided that HIV viral loads are undetectable and CD4 counts are sufficiently high (usually >500). Patient C's future, therefore, depends upon his tolerance of the regimen, his compliance with the treatment plan, and his body's response to therapy.

The patient will initially be followed on a monthly basis. The viral load will be checked one month after the initiation of therapy, then every three months thereafter. Liver profile, CBC, and amylase will be assessed after one month, then bimonthly. After three months, HIV and HBV quantitative PCRs will be measured. If both are well suppressed, follow-up will be extended to every two to three months. If the patient's liver function significantly deteriorates, supportive therapy for end-stage liver disease will be instituted.

FACULTY BIOGRAPHY

Jane C. Norman, RN, MSN, CNE, PhD, received her undergraduate education at the University of Tennessee, Knoxville campus. There she completed a double major in Sociology and English. She completed an Associate of Science in Nursing at the University of Tennessee, Nashville campus and began her nursing career at Vanderbilt University Medical Center. Jane received her Masters in Medical-Surgical Nursing from Vanderbilt University. In 1978, she took her first faculty position and served as program director for an associate degree program. In 1982, she received her PhD in Higher Education Administration from Peabody College of Vanderbilt University. In 1988, Dr. Norman took a position at Tennessee State University. There she has achieved tenure and full professor status. She is a member of Sigma Theta Tau National Nursing Honors Society. In 2005, she began her current position as Director of the Masters of Science in Nursing Program.

Mary Franks, MSN, APRN, FNP-C, is a board-certified Family Nurse Practitioner and NetCE Nurse Planner. She works as a Nurse Division Planner for NetCE and a per diem nurse practitioner in urgent care in Central Illinois. Mary graduated with her Associate's degree in nursing from Carl Sandburg College, her BSN from OSF Saint Francis Medical Center College of Nursing in 2013, and her MSN with a focus on nursing education from Chamberlain University in 2017. She received a second master's degree in nursing as a Family Nurse Practitioner from Chamberlain University in 2019. She is an adjunct faculty member for a local university in Central Illinois in the MSN FNP program. Her previous nursing experience includes emergency/trauma nursing, critical care nursing, surgery, pediatrics, and urgent care. As a nurse practitioner, she has practiced as a primary care provider for long-term care facilities and school-based health services. She enjoys caring for minor illnesses and injuries, prevention of disease processes, health, and wellness. In her spare time, she stays busy with her two children and husband, coaching baseball, staying active with her own personal fitness journey, and cooking. She is a member of the American Association of Nurse Practitioners and the Illinois Society of Advanced Practice Nursing, for which she is a member of the bylaws committee.

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ETHICAL DECISION MAKING

UPDATE

#37074 • 15 ANCC Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to assist healthcare professionals to define the predominant ethical theories and principles used in health care, determine any legal and regulatory implications, and in collaboration with their colleagues and patients/clients, make effective decisions that determine the appropriate course of treatment, or refusal of such, for and with those for whom they care.
Audience: This course is designed for all nurses and allied healthcare professionals.
Additional Approvals: AACN Synergy CERP Category B, CCMC

COMMON CONCERNS FOR PATIENTS WITH DEMENTIA

NEW!

#39060 • 1 ANCC / 1.2 Pharm Hours

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide nurses with an overview of the physical and psychosocial problems encountered by patients with dementia, so they might intervene to protect their well-being.
Audience: This course is designed for nurses in a variety of practice settings who work with older patients.
Additional Approvals: AACN Synergy CERP Category A

PULMONARY EMBOLISM

NEW!

#90120 • 2 ANCC / 1 Pharm Hour

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals with the knowledge and clinical strategies necessary to optimally triage and treatment patients with pulmonary embolism.
Audience: This course is designed for physicians, PAs, and nurses involved in assessing, triaging, and managing patients with suspected pulmonary embolism.
Additional Approvals: AACN Synergy CERP Category A

AGITATION, SEDATION, AND DELIRIUM IN ADULT ICU PATIENTS

NEW!

#90180 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide prescribers and other healthcare professionals with the knowledge and skills necessary to identify and act to avoid or address agitation, inappropriate sedation, and delirium in ICU patients.
Audience: This course is designed for physicians, physician assistants, and nurses involved in the care of patients in intensive care units.
Additional Approvals: AACN Synergy CERP Category A

PRESCRIBING OPIOIDS, PROVIDING NALOXONE, AND PREVENTING DRUG DIVERSION: THE WEST VIRGINIA REQUIREMENT

WV Mandate

#91603 • 3 ANCC / 3 Pharm Hours

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.
Audience: This course is designed for all physicians, physician assistants, nurses, and pharmacy professionals in West Virginia who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.
Additional Approvals: AACN Synergy CERP Category A
Special Approval: This course meets the one-time requirement for drug diversion training for APRNs authorized to prescribe.

FALLS AND FALL PREVENTION

NEW!

#91660 • 3 ANCC Hours

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of course is to provide healthcare professionals with the knowledge and skills necessary to intervene to reduce falls risk in their patients.
Audience: This course is designed for physicians, physician assistants, nurses, and allied professionals involved in the care of patients at risk for falls.
Additional Approvals: AACN Synergy CERP Category A

AUTISM SPECTRUM DISORDER

UPDATE

#92204 • 5 ANCC / 1 Pharm Hour

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to educate healthcare professionals about the epidemiology, diagnosis, and management of ASD. Additionally, this course will provide the information necessary to screen children seen in primary care for ASD in order to appropriately refer patients and their families for more expansive assessment and treatment referral as rapidly as possible in order to avoid unnecessary morbidity and mortality.
Audience: This course is designed for healthcare professionals in all practice settings who may be involved in the care of patients with an autism spectrum disorder.
Additional Approvals: AACN Synergy CERP Category A, CCMC

Prices are subject to change. Visit www.NetCE.com for a list of current prices.

Course Availability List *(Cont'd)*

MATERNAL HEALTH DISPARITIES

NEW!

#93010 • 4 ANCC Hours

Book By Mail – $32 • ONLINE – $24

Purpose: The purpose of this course is to provide healthcare providers with the knowledge and skills necessary to improve maternal outcomes in all races, ethnicities, and marginalized groups.

Audience: This course is designed for all healthcare providers who may intervene to improve peripartum and postpartum health care and reduce health disparities.

Additional Approvals: AACN Synergy CERP Category B

HEALTH ISSUES DISTINCTIVE TO WOMEN

UPDATE

#93314 • 15 ANCC / 5 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide healthcare professionals with updated information related to issues surrounding women across the lifespan to facilitate thorough and appropriate care.

Audience: This course is designed for nurses and other healthcare professionals involved in improving health outcomes for women.

Additional Approvals: AACN Synergy CERP Category A

LOW BACK PAIN

#94102 • 15 ANCC / 10 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide healthcare professionals with a greater understanding of the pathophysiology and differential diagnosis of low back pain conditions so they may effectively treat or manage low back pain, resulting in improved patient health, quality of life, and satisfaction.

Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of patients with back pain.

Additional Approvals: AACN Synergy CERP Category A, CCMC

PREDIABETES: AN OPPORTUNITY TO PREVENT DIABETES

UPDATE

#94194 • 15 ANCC / 7 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: Studies have shown that diabetes can be delayed or prevented in people with prediabetes, but risk reduction relies heavily on lifestyle changes on the part of the patients, making education and counseling of vital importance. The purpose of this course is to provide healthcare professionals with the information and skills necessary to effectively deal with this common condition and learn ways to help patients make healthy lifestyle choices.

Audience: This course is designed for nurses in adult primary care, clinical, and acute care settings, healthcare and behavioral health professionals in public health and preventive medicine settings, and health education specialists.

Additional Approvals: AACN Synergy CERP Category A

INFLUENZA: A COMPREHENSIVE REVIEW

UPDATE

#94424 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide healthcare professionals with an updated review of influenza, including clinical aspects, public health issues, and strategies for prevention. The goals are to minimize the burden of influenza on patients and communities, prevent complications and hospitalizations, and save healthcare dollars.

Audience: This course is designed to help healthcare professionals and allied personnel understand influenza and their role in its prevention.

Additional Approvals: AACN Synergy CERP Category A, CCMC

SUBSTANCE USE DISORDERS AND PAIN MANAGEMENT: DEA MATE ACT TRAINING

DEA MATE Act

#95300 • 8 ANCC / 8 Pharm Hours

Book By Mail – $56 • ONLINE – $48

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute controlled substances with an appreciation for the complexities of managing patients with substance use disorders and comorbid pain in order to provide the best possible patient care and to prevent a growing social problem.

Audience: This course is designed for all healthcare professionals who may alter prescribing practices or intervene to help meet the needs of patients with substance use disorders.

Additional Approvals: AACN Synergy CERP Category A, CCMC

Special Approval: This course meets the Alabama requirement for 4 BOM preapproved hours of pharmacology for QACSC-holders.

OPIOID SAFETY: BALANCING BENEFITS AND RISKS

AL Mandate

#95500 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.

Audience: This course is designed for all physicians, osteopaths, physician assistants, pharmacy professionals, and nurses who may alter prescribing and/or dispensing practices to ensure safe opioid use.

Additional Approvals: AACN Synergy CERP Category A, CCMC

Special Approval: This course meets the Alabama requirement for 4 BOM preapproved hours of pharmacology for QACSC-holders.

Prices are subject to change. Visit www.NetCE.com for a list of current prices.

Course Availability List *(Cont'd)*

ALZHEIMER DISEASE

UPDATE

#96154 • 15 ANCC / 1 Pharm Hour

Book By Mail – $98 • ONLINE – $90

Purpose: In order to increase and maintain a reasonable quality of life for patients with Alzheimer disease throughout the course of the disease, caregivers must have a thorough knowledge and understanding of the disease. The purpose of this course is to provide clinicians with the skills to care for patients with Alzheimer disease in any setting as part of the interdisciplinary team.

Audience: This course is designed for clinicians who come in contact with patients with Alzheimer disease in hospitals, long-term care facilities, home health care, and the office.

Additional Approvals: AACN Synergy CERP Category A, CCMC

ANXIETY DISORDERS

#96182 • 15 ANCC / 10 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to appropriately identify and treat patients with anxiety disorders, addressing knowledge gaps, enhancing clinical skills, and improving patient outcomes.

Audience: This course is designed for health and mental health providers involved in the identification, treatment, and care of patients with anxiety disorder.

Additional Approvals: AACN Synergy CERP Category A, CCMC

SUICIDE ASSESSMENT AND PREVENTION

#96442 • 6 ANCC Hours

Book By Mail – $44 • ONLINE – $36

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.

Audience: This course is designed for physicians, nurses, pharmacists, and other healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.

Additional Approvals: AACN Synergy CERP Category A, CCMC

CANNABINOID OVERVIEW

NEW!

#98010 • 3 ANCC / 3 Pharm Hours

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the various cannabinoids.

Audience: This course is designed for healthcare professionals whose patients are taking or are interested in taking cannabinoid products.

Additional Approval: AACN Synergy CERP Category A

DIETS AND DIETARY APPROACHES TO WEIGHT LOSS

NEW!

#98120 • 4 ANCC Hours

Book By Mail – $32 • ONLINE – $24

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to counsel patients regarding diets and dietary approaches to weight management.

Audience: This course is designed for for all physicians, nurses, and allied professionals involved in the care of patients who are interested in exploring dietary options to weight control.

Additional Approvals: AACN Synergy CERP Category A

CHRONIC PAIN SYNDROMES: CURRENT CONCEPTS AND TREATMENT STRATEGIES

UPDATE

#98703 • 15 ANCC / 12 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: Chronic pain imposes a distressing sensory and emotional experience on the patient and potentially leads to life-altering negative outcomes. The purpose of this course is to provide clinicians with the information necessary to identify and appropriately manage chronic pain syndromes in accordance with evidence-based guidelines.

Audience: This course is designed for physicians, nurses, physician assistants, and allied care providers in the primary care setting who may identify and treat patients with chronic pain syndromes.

Additional Approvals: AACN Synergy CERP Category A, CCMC

ANEMIA IN THE ELDERLY

UPDATE

#99084 • 5 ANCC / 2 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide primary care health professionals a review of pathophysiology, clinical assessment, and management of anemia in the elderly. The goal is to promote early diagnosis, appropriate treatment, and improved outcomes for the geriatric population.

Faculty: Susan Waterbury, MSN, FNP-BC, ACHPN

Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of elderly patients.

Additional Approvals: AACN Synergy CERP Category A, CCMC

GERIATRIC FAILURE TO THRIVE: A MULTIDIMENSIONAL PROBLEM

#99204 • 5 ANCC / 1 Pharm Hour

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to educate nurses, social workers, and other healthcare providers regarding geriatric failure to thrive and to promote evidence-based clinical practice when caring for patients with this condition.

Audience: This course is designed for nurses, nurse practitioners, and behavioral health professionals who work in or are interested in learning more about geriatrics. Other disciplines that may benefit from this training include dieticians, therapists, and psychologists.

Additional Approvals: AACN Synergy CERP Category A, CCMC

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12. Are you more confident in your ability to provide nursing care after completing this course?
13. Do you plan to make changes in your nursing practice as a result of this course content?

#94820
Chronic Cough in Adults
10 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#38910
Pathophysiology: The Hepatobiliary System
15 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#94820 Chronic Cough in Adults — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____
_____
_____
_____

#38910 Pathophysiology: The Hepatobiliary System — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____
_____
_____
_____

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