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Abstract
Ascites, the collection of fluid in the peritoneal cavity, can originate from hepatic, malignant, cardiac, renal, and infectious diseases. Cirrhosis, tuberculosis, and malignancy are the most common causes in Indian patients. Ultrasonography and paracentesis with ascitic fluid examination are the modalities used to establish the etiology. Sodium restriction and diuretics are mainstay of treatment of ascites due to cirrhosis. Ascites due to other causes requires specific treatment. For refractory ascites large volume paracentesis along with infusion of albumin is used. Liver transplantation is the gold standard therapy. Despite the advances in modern medicine, development of ascites is associated with poor prognosis and high mortality.

Introduction
Commonly presenting with abdominal swelling, ascites is a pathological fluid collection in the peritoneal cavity. The common causes of ascites are cirrhosis, tuberculosis, malignancy, cardiac failure, pancreatitis, and nephrotic syndrome. The management depends on the etiology of ascites from hepatic to extrahepatic causes and on the stage of ascites from uncomplicated to refractory stage.

Causes of Ascites
Various causes of ascites are shown in Table 1. In India, cirrhosis of liver is most common cause of ascites followed by tuberculosis versus malignancy in developed countries. Sometimes more than one condition may coexist with significant management implications. Alcoholic patients can have cirrhosis with cardiomyopathy, tuberculosis, or malignancy. For management, perspective ascites is grouped under two heads: ascites due to cirrhosis or due to causes other than cirrhosis.

Ascites Due to Cirrhosis
Portal hypertension and renal salt and water retention are the key mechanisms of ascites in cirrhosis. Ascites denotes the transition from a compensated to a decompensated stage of cirrhosis. Initially ascites is uncomplicated, not infected, and responds well to diuretics. As disease progresses, ascites ceases to respond to diuretics (refractory ascites) and renal dysfunction supervenes (hepatorenal syndrome).
Uncomplicated ascites is subdivided into three grades: mild, moderate, and massive ascites. Refractory ascites has two subtypes: diuretic-resistant and diuretic-intractable.

Complications of Cirrhosis
Spontaneous Bacterial Peritonitis
Spontaneous bacterial peritonitis (SBP), a lethal complication, results from ascitic fluid infection in absence of an intra-abdominal infective focus.
Hepatic Hydrothorax

Pleural effusion develops in approximately 5–10% of patients with cirrhosis due to transdiaphragmatic movement of fluid from peritoneal cavity to pleural space. Patients usually have minimal ascites. Pleural effusion is right sided in 85%, left sided in 13%, and bilateral in 2% cases.

Ascites due to Causes other than Cirrhosis

In malignancy and tuberculosis tumor cells and tubercles lining the peritoneum produce protein rich fluid. Pancreatitis, heart failure, nephrotic syndrome, and hypothyroidism may cause ascites.

Malignant Ascites

Malignant ascites occurs secondary to:
- Peritoneal carcinomatosis: malignant infiltration of peritoneum
- Massive hepatic metastasis
- Profound desmoplastic response to infiltrating breast cancer
- Chemotherapy induced nodular regenerative hyperplasia

Two-thirds cases of malignant ascites are caused by peritoneal carcinomatosis from adenocarcinomas of pancreas, stomach, colon, ovary, uterus, lungs, or breast. The remaining are caused by hepatocellular carcinoma or hepatic metastases.

Evaluation and Diagnosis

Clinical Assessment

Ascites may be asymptomatic or may just produce an increase in abdominal girth described as tightness of clothes or belt. Massive ascites produces abdominal discomfort, umbilical eversion, hernias, and breathlessness. Physical examination is not significant in mild ascites. In moderate ascites, flank dullness and shifting dullness are sensitive findings. Massive ascites produces marked distension of abdomen. Signs of liver disease and portal hypertension should be sought. Hepatic, renal, and cardiac status should be assessed.

Pathological Assessment

Routine urine examination, complete blood counts, blood sugar, liver function tests, viral markers (HBV, HCV, and HIV), serum creatinine, NT-Pro BNP, and thyroid function tests should be obtained.

Imaging

Ultrasound is the best modality to document the presence of ascites. It can provide information about cause of ascites (fibrosis in cirrhosis, nodules in HCC, or liver metastasis). Fibroscan is a new modality to document fibrosis of liver. Doppler sonography can detect portal or hepatic vein thrombosis. Contrast enhanced CT, echocardiography, upper GI endoscopy, and colonoscopy may be ordered in select conditions. MRI using gadolinium scan can demonstrate enhancement of peritoneal lining in peritoneal carcinomatosis.

<table>
<thead>
<tr>
<th>TABLE 1 Causes of ascites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Portal hypertension</strong></td>
</tr>
<tr>
<td>• Cirrhosis liver</td>
</tr>
<tr>
<td>• Alcoholic hepatitis</td>
</tr>
<tr>
<td>• Hepatic congestion</td>
</tr>
<tr>
<td>– Congestive cardiac failure</td>
</tr>
<tr>
<td>– Constrictive pericarditis</td>
</tr>
<tr>
<td>– Hepatic venous outflow obstruction</td>
</tr>
<tr>
<td>• Portal vein thrombosis</td>
</tr>
<tr>
<td>• Non-cirrhotic portal hypertension</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
</tr>
<tr>
<td>• Bacterial peritonitis</td>
</tr>
<tr>
<td>• Tubercular peritonitis</td>
</tr>
<tr>
<td>• HIV associated peritonitis</td>
</tr>
<tr>
<td><strong>Malignancies</strong></td>
</tr>
<tr>
<td>• Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>• Primary mesothelioma</td>
</tr>
<tr>
<td>• Hepatocellular carcinoma</td>
</tr>
<tr>
<td>• Metastatic liver disease</td>
</tr>
<tr>
<td>• Pseudomyxoma peritonei</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
</tr>
<tr>
<td>• Pancreatitis</td>
</tr>
<tr>
<td>• Hypoalbuminemia</td>
</tr>
<tr>
<td>• Nephrotic syndrome</td>
</tr>
<tr>
<td>• Lymphatic leakage</td>
</tr>
<tr>
<td>• Myxoedema</td>
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<tr>
<td>• SLE</td>
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</tbody>
</table>
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Approach to Ascites

Abdominal Paracentesis

Once the presence of ascites has been confirmed, the etiology of ascites is best determined by paracentesis. Between 20–50 mL of ascitic fluid should be aspirated and examined (Table 2).

Appearance

In ascites due to portal hypertension the fluid is clear and straw colored. Turbid fluid can result from infection or malignancy. Milky fluid, chylous ascites results from lymphatic disruption due to malignancy, trauma, and congenital abnormalities. Bloody ascites could be due to traumatic tap or malignant ascites. Blood in traumatic fluid clots but in malignant ascites does not clot.

Total Protein

Protein levels are useful in determining etiology of ascites. Traditionally ascitic fluid is grouped into:

- Exudate with protein concentration more than 2.5 g/dL.
- Transudate with protein concentration less than 2.5 g/dL.

Exudative ascites occurs secondary to peritoneal processes (malignancy, tuberculosis) or post-hepatic sinusoidal hypertension with normal sinusoids (heart failure, hepatic vein, or inferior venacava obstruction) whereas transudative ascites results from increased sinusoidal portal hypertension (cirrhosis). Total protein levels are also useful in determining susceptibility to infection. Patients with ascitic fluid protein less than 1.0 g/dL are prone to develop SBP.

TABLE 2
Tests of ascitic fluid

<table>
<thead>
<tr>
<th>Routine tests</th>
<th>Additional tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Gram stain and culture</td>
</tr>
<tr>
<td>Total protein</td>
<td>AFB smear, culture and adenosine deaminase activity</td>
</tr>
<tr>
<td>Serum ascites albumin gradient (SAAG)</td>
<td>Glucose and lactate dehydrogenase</td>
</tr>
<tr>
<td>Cell count</td>
<td>Amylase concentration</td>
</tr>
<tr>
<td></td>
<td>Cytology and carcinoembryonic antigen level</td>
</tr>
<tr>
<td></td>
<td>Triglyceride level</td>
</tr>
</tbody>
</table>

TABLE 3
Differentiation of ascites based on hepatic venous pressure gradient measurement

<table>
<thead>
<tr>
<th>Causes of ascites</th>
<th>WHVP</th>
<th>FHVP</th>
<th>HVPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>Increased</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Cardiac ascites</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Malignant ascites peritoneal tuberculosis</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

FHV, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; WHVP, wedged hepatic venous pressure

Serum-ascites Albumin Gradient

Serum-ascites albumin gradient (SAAG) is the difference between albumin concentration in the ascitic fluid and that in the serum both collected at the same time. It is a very useful tool to establish the presence of portal hypertension. A SAAG value more than 1.1 g/dL reflects portal hypertension and indicates the ascites is due to increased pressure in the hepatic sinusoids. The SAAG has been found to be superior to the total protein concentration for the differential diagnosis of ascites.

Hepatic Venous Pressure Gradient

Hepatic venous pressure gradient (HVPG) is direct measure of hepatic sinusoidal pressure measured via a catheter in right femoral or internal jugular vein. Portal hypertension is defined as HVPG value more than 6 mm Hg (Table 3).

Laparoscopy

Laparoscopy offers the advantages of visual inspection of the peritoneal cavity and obtains targeted biopsies for histological studies. With the availability of new imaging techniques, the need for laparoscopy in determining the cause of ascites has decreased.

Diagnostic Developments

New novel diagnostic markers such as leukocyte esterase reagent strips for diagnosing SBP, viscosity measurement of ascitic fluid to discriminate between portal and non-portal hypertension, vascular endothelial growth factor (VEGF), bacterial DNA for documenting bacterial translocation, and markers of poor prognosis such as endotoxin and peptidoglycan/β-glucan have been proposed but still need validation.
Approach to a Patient of New Onset Ascites
See Flowchart 1.

Evaluation of Infection

Cell Counts
A predominance of neutrophils indicates an acute intra-abdominal inflammation. An ascites PMN count greater than 250/mm³ establishes diagnosis of SBP. Predominant mononuclear cells indicate tubercular ascites.

Smear and Bacterial Culture
Culture samples of ascitic fluid for both aerobic and anaerobic bacteria should be inoculated at the bedside into a blood culture bottle.

Ascitic Fluid Glucose and LDH Levels
Ascetic fluid LDH higher than serum LDH (ratio >1.00) and ascetic fluid glucose below 50 mg/dL suggests secondary bacterial peritonitis.

Evaluation of Tubercular Ascites
In tuberculous peritonitis, the smear for acid-fast bacilli is rarely positive and culture is positive only in about 50% of cases. Polymerase chain reaction for MTB has a high sensitivity (94%). Adenosine deaminase activity (ADA) is a reliable marker of tuberculous ascites. Mononuclear cell predominant leucocytes >500/cc, total protein more than 3 g/dL, LDH >90 units/L, or ADA >36–40 IU/L has a sensitivity of 100% and a specificity of 97% for of peritoneal tuberculosis. Laparoscopy with peritoneal biopsy and histopathology is the gold standard for diagnosis of peritoneal tuberculosis. Recommended stepwise approach for the diagnosis of peritoneal tuberculosis is detailed in Flowchart 2.

Evaluation of Malignant Ascites
Abdominal ultrasound and CT may be useful to demonstrate the primary malignancy or hepatic metastases but seldom confirms the diagnosis of peritoneal carcinomatosis. Analysis of the ascetic fluid is the most important step in

Flowchart 1: Approach to a patient of new-onset ascites

Asc prot, ascites total protein level; CUS, cardiac echosonography, HVPG, hepatic vein pressure gradient
the diagnostic work-up (Table 4). Laparoscopy may be required to confirm the diagnosis.

**Treatment of Ascites**

**Ascites due to Causes other than Cirrhosis**

Treatment is to be directed at the underlying cause:

- **Infective ascites**: Appropriate antibacterial therapy
- **Tubercular ascites**: Anti-tubercular therapy along with large volume paracentesis for severe ascites
- **Pancreatic ascites**: Conservative measures like salt restriction and diuretics
- **Malignant ascites**: Does not respond to sodium restriction or diuretics. Large volume paracentesis (LVP), transcutaneous catheter placement, peritoneovenous shunt, and autopumps are used

**Treatment of Ascites due to Cirrhosis**

Except for liver transplant, none of the therapies improves the survival. However, treatment of ascites not only improves the quality of life but prevents SBP, a lethal complication. The development of ascites in a patient of
cirrhosis denotes a poor prognosis with a median survival of 1.5 years so these patients should be considered for liver transplant.

**Sodium Restriction and Diuretics**

According to the European Association for the Study of the Liver, patients with cirrhosis and grade 1 ascites do not need diuretics and a low sodium diet. In patients with grade 2 ascites, sodium consumption is restricted to 2 g sodium (5.2 g of dietary salt) per day along with diuretic therapy. The goal of diuretic treatment is a loss of weight up to 1.0 kg/day if both ascites and edema are present and up to 0.5 kg/day in patients with ascites alone. Spironolactone, an aldosterone antagonist, is preferred as the initial diuretic. Recommended starting dose is 50–100 mg/day. Addition of a loop diuretic, furosemide or torsemide, potentiates effect of spironolactone. The maximum dose of diuretics recommended is a combination of spironolactone 400 mg/day with furosemide 160 mg/day.

In patients with massive ascites, the method of choice is LVP followed by diuretic agents and a low sodium diet. Approach to a patient of new ascites has been summarized in Flowchart 3.

**Therapeutic Options for Refractory Ascites**

**Large Volume Paracentesis**

In normal clinical practice, the first-line therapeutic intervention is large volume paracentesis repeated every 2–3 week. Between 5–6 L of the ascitic fluid is removed in combination with I/V infusion of albumin (6–8 gm/L of fluid drained) to prevent paracentesis-induced circulatory dysfunction.

**Peritoneovenous Shunt**

Peritoneovenous shunt (PVS) drains ascitic fluid into the venous system. With laparoscope a shunt is placed from peritoneal cavity to superior vena cava close to
the entrance of right atrium. A valve at the venous end prevents backflow of blood into the tubing. PVS has been reported to improve glomerular filtration rate in patients with renal insufficiency. However, long-term results were worse due to infection, shunt thrombosis, disseminated intravascular coagulation, and air embolism.

**Surgical Portosystemic Shunt**

In portosystemic shunt the portal vein is used as an outflow tract to relieve portal hypertension. However, because of high surgical mortality, they are seldom used nowadays.

**Transjugular Intrahepatic Portosystemic Shunt**

Transjugular intrahepatic portosystemic shunt (TIPS) is a non-surgical portacaval anastomosis. In this procedure, a tract is created between branches of hepatic and portal veins. Portal pressure reduction improves renal blood flow and glomerular filtration rate. Current clinical guidelines recommend using TIPS only in patients who require frequent LVP.

**A Patient with Contraindications to TIPS**

- In malignant ascites implantation of a permanent PleurX tunneled peritoneal catheter allows drainage of small amount of ascitic fluid (<2 L/day) in small portions.13
- An automatic low-flow pump (Alfapump) moves ascitic fluid to the bladder in small portions (5–10 mL) every 5–10 min. It may serve as a “bridge” to liver transplantation.

**Liver Transplantation**

Liver transplantation is the definitive treatment for ascites, as it eliminates portal hypertension and all other accompanying complications of liver cirrhosis. Overall, 1 year survival after liver transplantation exceeds 75%. Approach to manage refractory ascites is shown in Flowchart 4.14
Novel Therapies in Refractory Ascites

**V2 Receptor Antagonists**
Satavaptan, a selective V2 vasopressin receptor antagonist, acts on the distal renal tubule to increase water excretion, making it an attractive novel drug for patients who do not respond to conventional diuretics.

**Vasoconstrictors**
Clonidine, a centrally acting $\alpha_2$-agonist, when used with spironolactone decreases the need for diuretics. Midodrine, an $\alpha_1$-adrenoreceptor agonist, increases sodium excretion in patients with cirrhosis and refractory ascites without azotemia. In an RCT by Hanafy et al., midodrine (15 mg/day) and rifaximin (1.1 g/day) added to diuretics, increased diuresis and improved short-term survival. Terlipressin, a V1 receptor agonist, improved the glomerular filtration rate and induced natriuresis in patients with cirrhosis and ascites without HRS. Despite the positive results of the aforementioned studies, the addition of clonidine or midodrine to the diuretic treatment in refractory ascites is not recommended by current guidelines.

**Conclusion**
Ascites, commonly presenting as abdominal swelling, is accumulation of free fluid in peritoneal cavity. Cirrhosis, tuberculosis, and malignancy are the common causes of ascites. Mild ascites is asymptomatic but large ascites causes abdominal discomfort and breathlessness. Ultrasonography detects the presence of ascites. Paracentesis with fluid examination establishes etiology of disease. Sodium restriction and diuretic therapy is the mainstay of cirrhotic ascites treatment. Ascites due to causes other than cirrhosis requires specific treatment. In refractory ascites, LVP with albumin infusions, TIPS, PVS, and automatic pumps are helpful. Liver transplantation is the gold standard therapy. Despite the advances in modern medicine, development of ascites is associated with poor prognosis and high mortality.

**References**
Abstract
Acute-on-chronic liver failure (ACLF) is a clinical syndrome characterized by hepatic and/or extra-hepatic organ dysfunction in a patient with chronic liver disease. Multiple definitions exist in the literature. Irrespective of the definition, ACLF is associated with high short-term mortality. The syndrome is dynamic, and daily estimation of prognostic scores and organ dysfunction can predict the prognosis. A multidisciplinary team involving hepatologists, liver transplant surgeons, intensive care specialists, radiologists and pathologists is essential for the comprehensive management of patients with ACLF. Early identification and treatment of the acute precipitant is as essential as intensive monitoring, nutrition, antibiotics, albumin, and supportive care for extra-hepatic organ dysfunction. Liver transplantation remains the definitive treatment, albeit with its limitations. Physicians need to recognize the entity early, refer to multidisciplinary care centers, explain the prognosis, and prime the family members for the need for liver transplantation.

Introduction
Acute-on-chronic liver failure (ACLF) syndrome is characterized by abrupt hepatic decompensation secondary to an acute insult in a patient with chronic liver disease, associated with high short-term mortality. Overall, there are more than 20 definitions of ACLF available in the literature. Different definitions of ACLF provided by the European association for the study of the liver-chronic liver failure (EASL-CLIF), Asian Pacific Association for the study of the liver (APASL), and North American Consortium for the Study of End-stage Liver Disease (NACSELD) in Asia, Europe, and the USA, respectively have led to more confusion, rather than unifying the recognition of this syndrome.\textsuperscript{1–4}

Definition
The overall concept of defining ACLF is to identify high-risk patients with high short-term mortality. The possible reasons for the different definitions of ACLF syndrome include different etiologies (acute precipitants and chronic liver disease), and different clinical presentations of hepatic and extra-hepatic insults. Comparison of the major definitions—including EASL-CLIF, APASL, and NACSELD and World Gastroenterology Organisation (WGO)—is shown in Table \textit{1}. An important difference is the inclusion of patients with chronic liver disease (all stages of fibrosis) in the APASL definition (Flowchart \textit{1}); in contrast, the EASL-CLIF and NACSELD definitions include patients with cirrhosis only. Patients with prior decompensation are excluded in the APASL definition, while they are included in the EASL-CLIF and NACSELD definitions.

Acute Decompensation vs. ACLF
Acute decompensation (AD) refers to an event in the natural history of cirrhosis characterized by the development of jaundice, ascites, variceal bleed, or encephalopathy. AD when associated with organ failure is defined as ACLF.
# TABLE 1  Comparison of various definitions of acute-on-chronic liver failure

<table>
<thead>
<tr>
<th>Basis of definition</th>
<th>CANONIC study—1343 prospectively included AD patients</th>
<th>Initial arbitrary cut-off of bilirubin and INR. 2019 consensus updated based on AARC data (&gt;3,300 cases)</th>
<th>Prospective, multicenter study—507 patients with infection</th>
<th>Expert group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td>OF essential Isolated renal failure or any combination (2 or more) of any 6 OFs</td>
<td>Liver failure essential—jaundice</td>
<td>Infection ≥2 OF</td>
<td></td>
</tr>
<tr>
<td>Time interval since acute insult and development of ACLF</td>
<td>3 months</td>
<td>Less than 4 weeks</td>
<td>? 30 days</td>
<td>Less than 3 months</td>
</tr>
<tr>
<td>Patient inclusion</td>
<td>Cirrhosis only Both compensated and decompensated</td>
<td>Chronic liver disease (any stage of fibrosis) Compensated cirrhosis</td>
<td>Cirrhosis only Both compensated and decompensated</td>
<td>Chronic liver disease (any stage of fibrosis)</td>
</tr>
<tr>
<td>Patient exclusion</td>
<td>HIV HCC beyond Milan criteria</td>
<td>HCC Prior decompensated cirrhosis</td>
<td>HIV Prior organ transplant Disseminated malignancy</td>
<td>-</td>
</tr>
<tr>
<td>Acute precipitants</td>
<td>Hepatic and extrahepatic both</td>
<td>Hepatic</td>
<td>Infection</td>
<td>Both hepatic and extra-hepatic</td>
</tr>
<tr>
<td>Prognostic models</td>
<td>CLIF-C ACLF Score</td>
<td>AARC Score</td>
<td>MELD, CLIF-C ACLF</td>
<td>Not defined</td>
</tr>
</tbody>
</table>

AARC, APASL ACLF research consortium; ACLF, acute-on-chronic liver failure; AD, acute decompensation; APASL, Asia Pacific Association for the study of liver diseases; CLIF-C, chronic liver failure-consortium; EASL, European Association for the study of liver; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HIV, human immunodeficiency virus; INR, international normalized ratio; MELD, model for end stage liver disease; NACSELD, North American Consortium for the study of end stage liver disease; OF, organ failure; SOFA, Sequential Organ Failure Assessment; WGO, World Gastroenterology Organisation.
Approach to ACLF

The definition of ACLF embodies the basic constituents of the syndrome—an acute precipitant on a background of underlying chronic liver disease leading to organ failure and high short-term mortality. Each of the constituents must be addressed separately (Flowchart 2).

Prognosis and Scoring Systems

The Child-Turcotte-Pugh (CTP) score and model for end-stage liver disease (MELD) do not accurately assess the risk of patients with ACLF. The EASL-CLIF and APASL divide ACLF into three grades of severity based on short-term mortality. As per the EASL-CLIF, the 28-day mortality in grade 1 ACLF [defined as single renal failure (creatinine >2.0 mg/dL) or any other single organ failure with renal dysfunction (creatinine 1.5–2 mg/dL)] is around 20–25%, grade 2 ACLF (2 organ failures) is 35–40%, and grade 3 ACLF (3 or more organ failures) is 70–80%. A linear score has been proposed CLIF-C ACLF (based on 6 organ failure scores, age, and total leukocyte count), which correlates with outcomes.

The APASL-ACLF-AARC score includes bilirubin, INR, hepatic encephalopathy (HE), lactate, and creatinine with an overall score ranging from 5 to 15. Based on the AARC score, ACLF is graded into grade 1 ACLF (score 5–7), grade 2 ACLF (8–10), and grade 3 ACLF (>10) with predicted 28-day mortality of 13%, 45%, and 86%, respectively.

While assessing prognosis in patients with ACLF, it is important to use the scores as defined by definition, that is, use AARC score, if ACLF is defined by APASL definition and EASL-CLIF C ACLF in patients defined by EASL-CLIF definition.

Dynamic Assessment of the Prognostic Score

ACLF is a dynamic syndrome; therefore, it is important to assess patients daily for changes in organ failures and scores. A change in the score helps in early detection of deterioration and warrants change in the management plan. Patients showing an improvement in the grade of ACLF over the first 3 days are associated with a better outcome. The grade of ACLF between day 3 and 7 predicts outcome better than the grade at presentation.
Role of Liver Biopsy

A liver biopsy is not routinely recommended in the management of patients with ACLF. It may be indicated when the diagnosis is unclear, clinical suspicion of autoimmune hepatitis, or Wilson disease. The presence of neutrophilic infiltration, bilirubinostasis, megamitochondria are markers of poor prognosis in alcoholic hepatitis. Since patients with ACLF often have concomitant ascites and coagulopathy, if indicated, a transjugular route is recommended over a percutaneous one.

Management

Management of Acute Precipitants

Withdrawal of the acute insult is essential to stall the inflammatory cascade (Fig. 1). Etiology specific interventions are effective. Patients with active alcoholism benefit from abstinence. It is unclear whether use of corticosteroids is associated with mortality benefit in patients with alcohol-related ACLF. Steroids are associated with increased risk of infections; their use needs to be individualized and justified in each case depending on the risk-benefit ratio. In patients with reactivation of hepatitis B presenting as ACLF, use of antiviral drugs such as tenofovir disoproxil fumarate (TDF) is associated with a better outcome. For hepatitis E virus infection, no specific therapy is recommended. Patients with autoimmune hepatitis (AIH)-ACLF without hepatorenal syndrome and sepsis can be considered for a trial of steroids. In patients with Wilson disease, chelation therapy is recommended. Also, consideration should be given to early liver transplantation (LT) in those categorized as likely to have poor prognosis, as documented by new Wilson Index of more than 11. Plasmapheresis can be tried as a bridge to LT in patients with fulminant presentation of Wilson disease.

Drugs are another important precipitant of ACLF. The common drugs include anti-tuberculosis therapy and complementary and alternative medicines. A detailed history of drugs should be elicited at presentations and all drugs should be stopped.

Patients with acute variceal bleed (AVB) need to be managed with resuscitation, splanchic vasoconstrictors and endoscopic therapy. In select cases, placement of preemptive (<72 hours of presentation) transjugular intrahepatic portosystemic shunt (TIPS) can be considered. Among patients with uncontrolled bleeding...
CHAPTER 114
Approach to Acute-on-Chronic Liver Failure

Fig. 1: The management approach to acute-on-chronic liver failure
rescue TIPS is an option, such patients usually have a poor outcome.

Bacterial infections are present in 10–30% of ACLF patients at admission, and another 30–50% may develop an infection during the hospital stay. Choice of empirical antibiotics depends on the setting. For community acquired infections a 3rd generation cephalosporin is a good choice. For nosocomial infections, piperacillin/tazobactam is preferred for areas with low-prevalence of multidrug resistance organisms (MDROs), while carbapenems are preferred in areas of high MDRO, with or without a gram positive glycopeptidase for areas of high methicillin resistant Staphylococcus aureus (MRSA). Appropriate antibiotics according to local sensitivity patterns need to be administered at the earliest once culture reports are available.5

Management of Extrahepatic Organ Failures

Renal

Acute kidney injury (AKI) in ACLF can arise due to structural as well as functional causes. The withdrawal of diuretics and volume expansion with albumin is the first step. Terlipressin and noradrenaline can be considered with data suggesting that the former is more effective in the management of the hepatorenal syndrome. Renal replacement therapy (RRT) indications include symptoms of uremia, volume overload, hyperkalemia, and metabolic acidosis. Continuous RRT involves very slow blood and dialysate infusion and is preferred in patients with hemodynamic instability. Alternatively, a shorter hybrid procedure called slow-low efficiency dialysis (SLED) can offer shorter procedure times of 6–12 hours, maintaining hemodynamic stability as well.

Cerebral

Management of HE includes evaluation and management of precipitants (Fig. 1). Hyperammonemia is associated with HE. Baseline hyperammonemia and persistent hyperammonemia are associated with poor outcomes in patients with ACLF. Lactulose and rifaximin are useful first-line drugs that help in reducing ammonia. The role of L-ornithine L-aspartate (LOLA), L-ornithine phenylacetate (LOPA), and sodium benzoate have not been studied in ACLF patients. Elective intubation to prevent aspiration may be considered in patients with advanced (grade 3 and 4) HE.

Coagulation

Prophylactic transfusion of plasma, based on the international normalized ratio (INR), is not recommended. Similarly, prophylactic transfusion of platelet may not be of use in the absence of active bleeding. Viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) should be used to guide transfusion in cases, which require an invasive procedure or develop bleeding complications.

Circulatory

In patients with circulatory failure, noradrenaline should be considered as a first-line agent. Vasopressin or terlipressin can be an alternative second line agent.

Respiratory

Respiratory failure should be managed with ventilatory support using either noninvasive ventilation or invasive ventilation, as tolerated, if the PaO2/FiO2 is less than 200. Low tidal volume lung protective ventilation should be considered, and therapeutic paracentesis done to aid in decreasing work of breathing.

General Management

ACLF patients should be managed in an intensive care unit (ICU). The higher mortality rate in ACLF should not deter physicians from providing ICU care. The overall outcomes in ACLF patients are similar to patients with other diseases, matched for the severity of the illness.

Nutrition is essential in patients with ACLF and a diet comprising of 35–40 kcal/kg/day and protein intake of 1.5 g/kg/day is recommended. Supplementation with trace elements and vitamins should be considered. The use of albumin is recommended for its oncotic effects in presence of renal failure, spontaneous bacterial peritonitis, prevention of post-paracentesis circulatory dysfunction, as well as for its anti-inflammatory and antioxidant pleiotropic effects. The uses of non-selective beta-blockers and carvedilol have been shown to be safe and their discontinuation is not recommended.

Definite Management

Liver Transplantation

LT is the definite management of ACLF. There are no validated criteria for appropriate selection of candidates.
for early LT. Early LT within the first week should be offered to those having poor prognosis at presentation (MELD >30 or AARC >10) without multiple organ failures and sepsis. Dynamic monitoring with prognostic scores may help in early identification of patients who are at risk for poor outcome. Recent data suggests that LT is feasible, even in ACLF-3 cases who have 5–6 organ failures and is associated with a 1-year survival rate of more than 80% as compared to less than 10% among those not transplanted. Optimal timing of LT is crucial to have the best outcomes.

There are no established delisting criteria for LT in ACLF; however, transplant is not recommended in the presence of active sepsis.

Emerging Therapies

**Artificial Liver Support Systems**
Molecular adsorption and recirculating system (MARS) and fractionated plasma separation and adsorption (FPSA-Prometheus) have not shown any survival benefit in ACLF. Bioartificial liver support systems that substitute detoxification, biotransformation, and synthetic function as well by utilizing either human hepatoblastoma cell lines or porcine hepatocytes are promising. The recent creation of 3D liver organoids using hepatic progenitor cells or induced pluripotent stem cells might evolve as options for therapeutic use in future.

**Plasma Exchange**
Plasma exchange appears to be promising in small series. RCTs are needed to evaluate its role in management of ACLF.

**Liver Regeneration**
Since human liver has a huge regenerative potential due to the presence of progenitor cells, as evidenced by rapid regeneration after donor hepatectomy, it can also recover following acute insults. Contrasting results have been reported with granulocyte-colony stimulating factor (G-CSF), RCTs are needed before routine recommendation. Both bone marrow and umbilical cord derived mesenchymal stem cells have shown improvement in liver function when transfused via a peripheral vein.

**Fecal Microbiota Transplantation**
Evolving data suggests a potential role in alcohol-related ACLF not eligible for steroids or LT. Presently FMT remains an experimental therapy and should not be used outside of clinical trials.

**Futility of Care**
If LT is not available or contraindicated, presence of four or more organ failure and a CLIF-C ACLF score more than 64 is associated with a high mortality approaching 100%. In such situations, relatives should be explained about the poor outcomes.

**Prevention of ACLF**
Prevention of ACLF is of paramount importance. This can be achieved by preventing the acute triggers such as viral hepatitis—by universal vaccination (hepatitis B) and secondary prophylaxis with antivirals, abstinence from alcohol, and careful consideration before prescription of hepatotoxic drugs. However, despite active search, the trigger may not be detectable in up to 40% cases and is often attributed to pathological bacterial translocation occurring due to a combination of increased gut permeability and dysbiosis. Potential therapies targeting this aspect of pathogenesis are being evaluated.

**The Role of a Physician**
It is important for physicians to identify patients with poor prognostic factors early, so that they can be referred to higher centers for further treatment. Patients with ACLF should ideally be managed at a center with a multidisciplinary team comprising of hepatologists, gastroenterologists, LT surgeons, and critical care specialists. About one-third of patients reaching a referral hospital have an evidence of bacterial infection, making them poor candidates for LT. Hence, it is important to refer patients early, when they can still undergo LT. It is also the responsibility of the referring physician to explain the prognosis and prime the relatives to the need of LT.

**Conclusion**
It is essential to recognize ACLF as a distinct entity with high short-term mortality and potential reversibility. Prompt recognition and treatment strategy can result in a transplant-free survival of close to 50%.
References

Abstract
Dyspnea is a very common complaint encountered by medical professionals working both in general medical outpatient practice and also in emergency setup. Pulmonary and cardiac etiology are most commonly encountered; however, other causes like hematological or psychogenic causes are not very uncommon. A prompt and accurate diagnosis requires meticulous examination followed by proper use of investigative tools as per protocol.

Introduction
Dyspnea is a common presenting symptom that is encountered by clinician in everyday practice. It is said to be chronic if it is present for more than 4 weeks. Dyspnea is a debilitating symptom that affects the overall quality of life, exercise tolerance, morbidity, and mortality in various disease states. It is a better predictor of mortality than angina in patients with cardiac disease and forced expiratory volume in 1 second (FEV1) in patients with chronic pulmonary disease. In patients with chronic obstructive pulmonary disease (COPD) and sedentary adults, chronic dyspnea leads to low adherence to exercise training programs, decreased functional status, and poor psychological health.

The exact mechanisms of dyspnea are still not very well understood. Several recent studies have emphasized on the multidimensional nature of dyspnea. The perception of dyspnea depends on varying cortical integration of several afferent and efferent signals that involves a complex chain of events.

Chronic dyspnea is most frequently either due to respiratory or cardiac cause. However, in about one third of cases, the etiology is multifactorial. COPD, cardiac failure, asthma, ischemic heart disease, interstitial lung disease (ILD), and impaired psychological condition are some of the most common causes of chronic dyspnea.

Definition
The American Thoracic Society (ATS) defines dyspnea as "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioral responses." The ATS statement also reiterates the importance of self-reporting by patients, as dyspnea can be perceived only by the person experiencing it.

Epidemiology
It is difficult to ascertain the exact prevalence of chronic dyspnea in general population as different studies incorporate both acute and chronic dyspnea. Individuals above age of 70 years have higher prevalence of chronic dyspnea. Studies have shown that almost half of the patients admitted to acute tertiary care hospitals and
one-fourth of patients in ambulatory settings present with dyspnea. The prevalence of mild to moderate dyspnea ranges from 9% to 13% in adults according to some population-based studies. This figure is around 25–27% in persons older than 70 years.

Clinical Assessment
A proper history and clinical examination is of utmost importance. More than two-thirds of the patients need diagnostic testing beyond clinical examination. The initial clinical assessment of a patient with chronic dyspnea is directed toward determining the underlying cause, which is fundamental for management and subsequent referral to a specialist if needed. According to a study amongst patients with chronic dyspnea who were referred to a specialist cardiologist or respiratory clinic at a tertiary center, only 51% were appropriately referred as per their final diagnosis. This improper initial referral leads to significant delays in final diagnosis.

The history and findings from physical examination have low positive predictive value (PPV) individually and are more useful as negative predictive factors. However, usually the clinical findings are considered in combination, hence they are more likely to provide greater diagnostic accuracy.

History
The history given by the patient in his own words is of utmost importance. The effect of position, environmental stimuli, timing, aggravating, and relieving factors are helpful in arriving at a provisional diagnosis. For example, orthopnea indicates congestive heart failure (CHF), and nocturnal dyspnea is suggestive of CHF or Asthma. Chronic persistent dyspnea is suggestive of COPD, ILD, and chronic thromboembolic disease. A previous history of drug induced or occupational lung disease, ischemic heart disease is very vital. If the patient complains of dyspnea in the upright position with relief in supine position, that is, platypnea, it could be suggestive of left atrial myxoma or hepatopulmonary syndrome.

Physical Examination
A thorough physical examination is imperative for assessment of cause, severity and proper management. It starts during history taking itself when the patient’s ability to complete full sentence while talking is observed. Clinical signs of pallor, cyanosis, clubbing, and pedal edema are important. The symmetry of chest wall movements with respiration should be observed.

The hemodynamic stability of patient is confirmed by measuring the vital signs. Pulsus paradoxus (i.e., decrease in systolic blood pressure of more than 10 mm Hg during inspiration) could be due to cardiac causes such as pericardial disease, restrictive heart disease, or cardiac tamponade. Pulmonary disease such as COPD, asthma, large bilateral pleural effusion, tension pneumothorax, and pulmonary embolism may also be present with pulsus paradoxus. Increased work of breathing is evident by supraclavicular retraction, use of accessory muscles of respiration and sitting with the hands braced on knees, that is, tripod position. These signs are indicative of increased airway resistance or stiffness of lungs and chest wall.

Dullness on percussion of chest wall is indicative of pleural effusion. Likewise hyperresonance is a sign of emphysema or pneumothorax. On auscultation, wheeze, crepitations, and diminished breath sounds are vital clues to the etiological diagnosis.

In a study done by Pratter et al., an algorithmic approach to diagnosis of chronic dyspnea was found to be helpful in correct diagnosis in 99% of the cases. At the initial visit, the patient underwent Tier 1 testing and subsequently the clinician made a diagnosis. Patient was subjected to Tier 2 and 3 testing if needed (Flowchart 1, Table 1).

There are various scales to measure dyspnea, but the two most commonly used are Medical Research Council Scale for pulmonary disease and New York Heart Association functional classification for cardiac diseases (Table 2 and Box 1).

Investigations
A number of diagnostic tools may be helpful in the initial the workup of a patient with chronic dyspnea.
CHAPTER 115
Approach to a Patient with Chronic Dyspnea of Undetermined Etiology

Flowchart 1: Algorithm for evaluation of a patient presenting with dyspnea

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Algorithm for evaluation of a patient presenting with dyspnea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• History and physical examination</td>
</tr>
<tr>
<td></td>
<td>• Mahler baseline dyspnea index</td>
</tr>
<tr>
<td></td>
<td>• Lab investigations - CBC, TSH, BNP, blood chemistry</td>
</tr>
<tr>
<td></td>
<td>• PFT - Spirometry, lung volumes by plethysmography, diffusing capacity (DLCO), and a methacholine bronchoprovocation challenge (BPC)</td>
</tr>
<tr>
<td></td>
<td>• Chest X-ray</td>
</tr>
<tr>
<td>Tier 2</td>
<td>Cardiopulmonary exercise testing (CPET)</td>
</tr>
<tr>
<td>Tier 3</td>
<td>• Pulmonary:- CT scan of chest, bronchoscopy, thoracentesis, V/Q scan</td>
</tr>
<tr>
<td></td>
<td>• Cardiology:- Stress echocardiography, coronary catheterization</td>
</tr>
<tr>
<td></td>
<td>• Upper GI endoscopy, etc.</td>
</tr>
</tbody>
</table>

Table 1: Causes of dyspnea

<table>
<thead>
<tr>
<th>Type</th>
<th>Subtype</th>
<th>Probable diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Airways</td>
<td>COPD, asthma, bronchiectasis, airway mass, vocal cord dysfunction</td>
</tr>
<tr>
<td></td>
<td>Interstitial</td>
<td>ILD, passive congestion, malignancy, radiation exposure</td>
</tr>
<tr>
<td></td>
<td>Alveolar</td>
<td>Chronic pneumonia, malignancy, emphysema</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Pulmonary emboli, PAH</td>
</tr>
<tr>
<td></td>
<td>Extrinsic</td>
<td>Pleural effusion, obesity, kyphoscoliosis</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Myocardial</td>
<td>Ischemic heart disease, cardiomyopathy, HFrEF, HFpEF</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia</td>
<td>Atrial fibrillation, tachycardia, bradycardia</td>
</tr>
<tr>
<td></td>
<td>Pericardial</td>
<td>Restrictive/Constrictive pericarditis, pericardial effusion</td>
</tr>
<tr>
<td></td>
<td>Valvular</td>
<td>Aortic stenosis/Aortic regurgitation/Mitral stenosis/Mitral regurgitation</td>
</tr>
<tr>
<td></td>
<td>Congenital heart disease</td>
<td>Intracardiac shunt, Eisenmenger syndrome</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Neurogenic</td>
<td>Diaphragmatic paralysis, GB syndrome, myasthenia gravis, ALS</td>
</tr>
<tr>
<td></td>
<td>Muscular</td>
<td>Muscular dystrophy, myositis, metabolic abnormalities, thyroid disease</td>
</tr>
<tr>
<td>Other causes</td>
<td>Anemia</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>Pleural disease, postoperative period</td>
</tr>
<tr>
<td></td>
<td>Psychological</td>
<td>Anxiety, depression, hyperventilation</td>
</tr>
</tbody>
</table>

ALS, amyotrophic lateral sclerosis; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension.
TABLE 2 Medical Research Council Dyspnea Scale

<table>
<thead>
<tr>
<th>MRC Dyspnea Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Breathless only with strenuous exercise</td>
</tr>
<tr>
<td>• Short of breath when hurrying on the level or up a slight hill</td>
</tr>
<tr>
<td>• Slower than most people of the same age on a level surface or have to stop when walking at my own pace on the level</td>
</tr>
<tr>
<td>• Stop for breath walking 100 meters or after a walking few minutes at my own pace on the level</td>
</tr>
<tr>
<td>• Too breathless to leave the house or breathlessness while dressing or undressing</td>
</tr>
</tbody>
</table>

BOX 1 NYHA Classification
A. Class I: Symptoms with more than ordinary activity
B. Class II: Symptoms with ordinary activity
C. Class III: Symptoms with minimal activity
   1. Class IIIa: No dyspnea at rest
   2. Class IIIb: Recent dyspnea at rest
D. Class IV: Symptoms at rest

Chest Radiography
After initial clinical assessment, chest X-ray is the most valuable tool for diagnosis. Hyperinflated lung fields are suggestive of chronic obstructive lung disease. Low lung volumes are seen in interstitial edema or fibrosis, diaphragmatic dysfunction or impaired wall motion. The evidence of interstitial disease, pulmonary infiltrates should be looked in pulmonary parenchyma. Pulmonary venous hypertension is suggested by prominent pulmonary vasculature in upper zones. Enlarged central pulmonary arteries suggest pulmonary arterial hypertension (PAH). Enlarged cardiac shadow could be due to dilated cardiomyopathy or valvular heart disease. CHF may present as bilateral pleural effusion on X-ray. Unilateral effusion may be due to carcinoma, pulmonary embolism, parapneumonic effusion, or even heart failure.1,3

Laboratory Investigations
A complete blood count is essential to assess the hemoglobin levels for anemia, which may cause dyspnea or polycythemia, which may indicate chronic hypoxemia. B-type natriuretic peptide detects cardiomyocyte strain. Hence, this can be used to differentiate between cardiac and respiratory causes of dyspnea. Chronic respiratory failure may cause carbon dioxide retention resulting in elevated bicarbonate levels. Here arterial blood gas (ABG) analysis may prove to be useful.3,7

Electrocardiography
An electrocardiogram (ECG) is a relatively cheap and readily available investigation that may suggest any underlying cardiac problem, which may be the cause for dyspnea. It may show evidence of ischemic heart disease, prior myocardial infarction resulting in systolic dysfunction, or valvular heart disease. In a study done amongst patients with chronic dyspnea, 8% were found to have atrial fibrillation on ECG. Among these patients 80% were later diagnosed as having dyspnea due to an underlying cardiac disease.1

Spirometry
Spirometry is a useful test for detecting obstructive and restrictive ventilatory defects. It is especially useful when airway diseases such as bronchial asthma or COPD are suspected. However, it is underused in clinical practice due to lack of time and resources. In a study of patients with chronic dyspnea in primary care setting, the diagnostic accuracy after clinical assessment was 55%, which increased to 72% after spirometry test.1,2

Echocardiography
Echocardiography is a vital tool to assess cardiac structure and function. In patients with chronic dyspnea, echocardiography can identify conditions such as heart failure (HFrEF), ischemic heart disease, valvular heart disease, pulmonary hypertension, and pericardial pathology. According to recommendations from International Heart Failure guidelines, echocardiography should be done at the earliest during the diagnostic workup of high-risk patients with chronic dyspnea. It is
noninvasive, can be easily performed even at the bedside in ICU or ER and has no side effects like radiation in CT scan.

**Ultrasound**

Chest ultrasound provides a wealth of information and it can be performed quickly and easily in critically ill patients. It has a higher diagnostic accuracy than a combination of physical examination and chest X-ray. Various patterns such as in acute interstitial syndrome, pneumothorax, pleural effusion, consolidation, etc. can be identified. It avoids ionizing radiation, and hence is quite safe. Lung ultrasound can also be used to guide fluid management and perform therapeutic procedures such as thoracocentesis.\(^\text{10}\)

**Chest Computed Tomography (CT)**

CT scan of chest is most commonly used after an abnormal chest X-ray. It has a high sensitivity for diffuse parenchymal lung disease. It is also helpful in early detection of ILD or pulmonary emphysema. Although it is not the recommended modality, but still cardiomegaly and pulmonary edema can also be detected on CT chest. The only disadvantage of CT scan is the risk of radiation exposure. Hence, careful patient selection with assessment of risk and benefits should be done by the clinician prior to the CT scan. CT pulmonary angiography (CTPA) can be used to detect acute pulmonary embolism or chronic thromboembolic pulmonary hypertension (CTEPH).

**Advanced Respiratory Function Tests**

The advanced respiratory function tests are also valuable in detecting chronic dyspnea of respiratory etiology. The diffusing capacity of lung for carbon monoxide (DLCO) assesses the ability of lungs to transfer oxygen to blood. DLCO can be reduced both in PAH and ILD. DLCO in isolation is not sufficient to confirm or differentiate between the above two conditions. DLCO may predict mortality in a number of lung diseases, severe PAH, cancer, and various ILDs.\(^\text{1}\)

Test for bronchial hyperresponsiveness by broncho-provocation helps in diagnosis of patients with suspected asthma having normal spirometry. A study showed hyperresponsiveness to challenge testing in 34% of patients with chronic dyspnea. Among these 69% were diagnosed with asthma or COPD.\(^\text{1,3}\)

**Tertiary Investigations**

Depending upon the results of initial investigations, more specialized investigations are done if needed to determine the cause of chronic dyspnea. Imaging modalities such as cardiac MRI, CT, coronary angiography, stress echocardiography, lung ventilation/perfusion (V/Q) scan are done if required. Coronary angiography may also be done for assessment of coronary artery disease or pulmonary pressure. Bronchoscopy, muscle biopsy, or surgical lung biopsy are other tools. A FeNO test, or exhaled nitric oxide test, determines the lung inflammation and its suppression with steroids in patients with allergic or eosinophilic asthma.\(^\text{11}\)

**Cardiopulmonary Exercise Test (CPET)**

In patients having dyspnea, which is out of proportion to known cardiorespiratory disease, CPET can provide valuable information. It involves incremental testing of exercise capacity while the patient is seated and continuously monitored on a stationary bicycle. CPET measures intake of oxygen, elimination of carbon dioxide, and minute ventilation, while exercising on the bicycle. It is helpful in confirming the diagnosis of psychogenic dyspnea. In a study among patients with chronic dyspnea, 90% with normal CPET results were diagnosed to be having a non-cardiorespiratory cause for dyspnea.\(^\text{12}\)

**Treatment**

The optimal approach in the treatment of chronic dyspnea involves interventions that reduce the ventilatory demand, improve ventilatory capacity and respiratory mechanics and take care of the psychogenic aspect as well. Supplemental \(O_2\) is usually given if resting \(O_2\) saturation level is below 88% or if the saturation falls to this level with work or sleep. Supplementary oxygen has shown to improve mortality, especially in patients with COPD.\(^\text{2,3}\)

Multiple interventions are often required and they may have additive or synergistic effects. Some of these interventions include oxygen therapy, bronchodilators, noninvasive ventilation, exercise training, lung volume reduction surgery, etc.

Opiates alter affective component of dyspnea and reduce the respiratory drive. Psychological counseling, behavioral therapy, and anxiolytics have favorable effects on affective dimension of chronic dyspnea. An important
component of dyspnea management is cardiac and pulmonary exercise training.

Conclusion

The diagnosis of patients presenting with chronic dyspnea in primary or tertiary care is challenging. Chronic dyspnea is most common due to a cardiorespiratory cause. However, one third of patients have multifactorial etiology. Common comorbidities such as obesity and deconditioning often contribute to symptomatology. This increases diagnostic difficulty and problems in management. Evidence-based algorithms are helpful to improve the diagnosis and subsequent management of patients presenting with chronic dyspnea.

References

Abstract
In their everyday clinical practice, doctors are faced with decisions related to investigations, interventions, or therapeutic options. These decisions are sometimes routine and simple, but may be complicated on other occasions. Clinical decision-making is challenging because, these decisions are not only unavoidable but also must be made under uncertain conditions. Mathematics underlying decision-making includes basic mathematical language of probability and Bayes’ theorem. Understanding these mathematical principles and judicious application of diagnostic reasoning can help clinicians in arriving at the appropriate course of action in a rational, scientific, and objective way.

Introduction
Clinicians have to make decisions in daily practice either regarding the choice of diagnostic testing or regarding therapeutic options or interventions. These decisions are unavoidable, and are often made intuitively under uncertain conditions and, therefore, constitute a significant challenge. In this chapter we have attempted to provide an overview regarding the mathematics behind decision-making.

Basic Mathematics
To understand the science of clinical decision-making, an understanding of the basic mathematical language of probability and Bayes’ theorem is essential. Bayes’ theorem is a mathematical rule that defines how existing beliefs should be revised or modified when new evidence becomes available.1-3

Probability
In the context of clinical decision-making, probability is defined as a measure of the belief regarding the occurrence of an event. Mathematically, probability of an event A occurring is denoted as P[A] and is read as “P of A”; this value ranges from 0.0 to 1.0.4

Summation Principle
If in a given clinical situation, let us assume that four possible outcomes A, B, C, and D can occur by chance. The summation principle states that the “sum of probabilities” of all these four possible chance events (outcomes) equals 1.0.4 This is mathematically written as:

\[ P[A] + P[B] + P[C] + P[D] = 1 \]

Joint Probability
The concomitant occurrence of a number of events is termed as “joint probability” of occurrence of those events.4 The joint probability of occurrence of two events A and B is expressed as P[A,B].

Conditional Probability
The probability that an event A occurs, given that the event B is known to occur is termed “conditional probability” of
event A given occurrence of event B. This is expressed in statistical notation as $P[A \mid B]$. We can also express the relationship between joint and conditional probabilities by the following formula:

$$P[A \text{ and } B] = P[A \mid B] \times P[B]$$

**Independence**

In a clinical situation, if the “conditional probability” of event A, given that event B occurs, is identical to the “unconditional probability” of event A occurring, then, the events A and B are probabilistically considered to be independent.

This relationship is expressed as:

$$P[A \mid B] = P[A]$$

The “joint probability” of occurrence of independent events is governed by the “product rule” which states:

$$P[A, B] = P[A] \times P[B]$$

**Summation Principle for Joint Probabilities**

The summation principle for joint probabilities states that if $B_1$, $B_2$, $B_3$, and $B_4$ are mutually exclusive events (i.e., only one of these can occur), and $A$ is another event, then, probability of occurrence of event $A$ is given by the formula:


For computing the probability of an event from several conditional probabilities, the “averaging out” method is used.

**Bayes’ Theorem**

In clinical practice, diagnostic tests are performed to ascertain the definitive diagnosis. The possible results that are obtained on performing such a diagnostic test are listed in Figure 1 and Table 1. The performance of the diagnostic test is evaluated using a “gold standard” for categorization of the subjects as “having disease” or “no disease.” In this situation, Bayes’ theorem can be applied to estimate the probability of the disease given a positive or a negative test result. Generally, the possibilities of two disease states (disease is present/absent) are considered. However, several disease states $D_1$, $D_2$, and so on (up to $D_n$) can also be considered. Then, by applying Bayes’ theorem, the revised probability of any one disease ($D_i$) occurring given the test result $R$ can be calculated using the formula:

$$P[D_i \mid R] = \frac{P[R \mid D_i] \times P[D_i]}{\sum_{i=1}^{n} P[R \mid D_i] \times P[D_i]}$$

**Odds**

Odds of an event are defined by the number of occurrences divided by the number of non-occurrences. For example, odds of a disease = No. of persons who develop disease during follow-up/No. of persons who do not develop disease.

If $p$ is the probability of an event occurring, then, the probability that the event will not be occurring is denoted as $(1−p)$. Then, the odds favoring the occurrence of the event are calculated as $p/(1−p)$; and the odds against the event occurring are calculated as $(1−p)/p$.

Bayes’ theorem can also be expressed in terms of odds as:

$$P[D+ \mid R] = \frac{P[R \mid D+]}{P[R \mid D−]}$$

**Likelihood Ratio**

The likelihood ratio (LR) of a positive test result is the ratio of the probability of occurrence of the test result in persons with or without the disease.

$$LR = \frac{P[R \mid D+]}{P[R \mid D−]}$$
Similarly, LR for a negative test result = \(\frac{1-\text{sensitivity}}{\text{specificity}}\)

Post-test odds can be computed from the “pre-test odds” and LR, using the formula:

\[
\text{Post-test odds} = \text{pre-test odds} \times \text{LR}
\]

Some Applications of Bayes’ Theorem in Clinical Medicine

Some of the applications of the aforementioned mathematical principles that are used in clinical medicine for decision-making\(^3\),\(^5\),\(^6\) are briefly described below.

Receiver-operator Characteristic Curve

The receiver-operator characteristic (ROC) curve is plotted with 1-specificity (false positive rate) on the X-axis against sensitivity on the Y-axis. The ROC curve graphically portrays the trade-off between sensitivity and specificity for different chosen criteria (cut-off values) of positivity for the test result\(^4\),\(^7\),\(^8\) and facilitates the identification of the optimum threshold or cut-off value (Fig. 2, thick arrow). Some examples for the use of ROC curve analysis in decision-making include, defining the cut-off value of carotid intima media thickness as a surrogate marker for subclinical atherosclerosis,\(^8\) glycosylated hemoglobin (HbA\(_{1c}\)) for the diagnosis of diabetes mellitus,\(^9\) among others.

![Image of ROC curve](image)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Probabilities associated with the test results shown in Figure 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td><strong>Probability notation</strong></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>(P[T+ \mid D+])</td>
</tr>
<tr>
<td>Specificity</td>
<td>(P[T- \mid D-])</td>
</tr>
<tr>
<td>False-negative rate</td>
<td>(P[T- \mid D+])</td>
</tr>
<tr>
<td>False-positive rate</td>
<td>(P[T+ \mid D-])</td>
</tr>
<tr>
<td>Predictive value of positive test</td>
<td>(P[D+ \mid T+])</td>
</tr>
<tr>
<td>Predictive value of negative test</td>
<td>(P[D- \mid T-])</td>
</tr>
</tbody>
</table>

FN, false negative; FP, false positive; TN, true negative; TP, true positive

---

**Fig. 2:** Receiver-operator characteristic (ROC) curve along with 95% confidence bands (dotted lines). The ROC curve represents a graphical description of the “dynamic trade-off” between more accurate identification of subjects with disease versus those without disease. Each point on the ROC curve represents a potential cut-off value with an associated sensitivity. Area under the ROC curve (AUC) is a measure of the overall performance and ranges between 0 and 1. The line segment drawn from \((0,0)\) to \((1,1)\) represents the chance diagonal and this has an AUC = 0.5. Therefore, a diagnostic test with an AUC greater than 0.5 is better than “pure chance” in correctly categorizing a cut-off
**Decision Analysis**

While evaluating patients in everyday practice, a clinician takes into consideration the data obtained from the history and physical examination findings. On the basis of information thus gathered, clinicians, based on their previous experience and intuitive thinking, formulate a diagnostic work-up plan. Even though this intuitive approach has the advantage of being flexible, it is subjective and varies between various clinicians.

“Clinical decision analysis” approach has remarkably influenced decision-making in a rational way under conditions of uncertainty and has facilitated choosing the best possible course of action. It is an explicit, quantitative and prescriptive approach to clinical decision-making. In this approach, probabilities of arriving at a choice or chance decision, utility of the outcome from each of the options are considered and logical structure of the problem called “decision tree” is constructed. The decision tree is analyzed by considering the probability of each outcome along with its associated utility and the path with the highest expected value is chosen to arrive at a clinical decision. Clinical decision analysis has been applied in various commonly encountered clinical situations to arrive at a decision.

**Conclusion**

Clear understanding of the mathematics underlying decision making and judicious application of diagnostic reasoning can help clinicians in arriving at the appropriate course of action in a rational, scientific and objective way.

**References**

Abstract

Syncope, characterized by transient loss of consciousness due to cerebral hypoperfusion, is a common clinical condition requiring emergency medical attention. Emergency room approach to syncope entails its diagnosis and differentiation from other causes of transient loss of consciousness such as epilepsy, vertebrobasilar insufficiency, hypoglycaemia and psychiatric illnesses; risk stratification into high- and low-risk etiologies; and management. Vasovagal syncope and syncope due to orthostatic hypotension, which carry low-risk, usually have uneventful outcomes. Syncope due to underlying cardiac causes is usually difficult to diagnose and carry a poorer prognosis, and commonly requires hospitalization for further evaluation and management. In developed countries having well-equipped syncope units, most cases of syncope can be managed and discharged from the emergency room. However, in developing countries like India, lacking such facilities, high-risk cases of syncope should ideally be hospitalized for further evaluation and management.

Introduction

Syncope is the loss of consciousness (LOC) occurring transiently due to cerebral hypoperfusion. It is characterized by a rapid onset of the LOC, which occurs for a short duration, with a spontaneous complete recovery. Syncope is a common presenting problem, accounting for 1–3% of all emergency department visits with up to 50% being hospitalized. The LOC is associated with a brief period of actual or apparent LOC, along with loss of awareness during this period of unconsciousness, associated with abnormal motor control and loss of responsiveness. Transiently occurring LOC (T-LOC) can be due to either head trauma, or can be due to non-traumatic causes. Syncope falls under the latter group, but has to be differentiated from other conditions within this sub-group of non-traumatic causes, important among these are various forms of generalized seizures; psychogenic causes like psychogenic pseudosyncope, and non-epileptic seizure; vertebrobasilar insufficiency, hypoxemia, narcolepsy with cataplexy; and hypoglycemia. The term presyncope is commonly used to describe a condition resembling the prodrome of syncope, but which is not followed by actual LOC, probably because the hypoperfusion of the brain in presyncope does not result in LOC. Most of the times syncope presents as a medical emergency necessitating prompt management in the emergency ward. However, differentiating it from the other common causes of T-LOC, as well as identifying patients with syncope with potentially life threatening etiologies poses as a challenge in management especially in the emergency room (ER) settings. Therefore, the main focus should be in diagnosing syncope, differentiating it from other common causes of T-LOC and its risk stratification for hospitalization and optimum management.
### TABLE 1

**Types of syncope with underlying mechanism and causes**

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurally mediated (reflex or vasovagal)</td>
<td>Transient alteration in reflexes maintaining cardiovascular homeostasis</td>
<td>Vasovagal syncope</td>
</tr>
<tr>
<td></td>
<td>Transient vasodilatation/loss of vasoconstrictor tone plus bradycardia</td>
<td>Reflex syncope, e.g.:</td>
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<tr>
<td></td>
<td>with resultant loss of blood pressure control</td>
<td>- Post-micturition syncope</td>
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<tr>
<td></td>
<td></td>
<td>- Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Carotid sinus syndrome</td>
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<tr>
<td></td>
<td></td>
<td>- Ocular</td>
</tr>
<tr>
<td>Syncope due to orthostatic hypotension</td>
<td>Sympathetic vasoconstrictor failure ± failure of compensatory tachycardia</td>
<td>Primary autonomic failure</td>
</tr>
<tr>
<td></td>
<td>with resultant hypotension on standing</td>
<td>Peripheral neuropathy with secondary autonomic failure, e.g.:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Drug-induced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Volume depletion</td>
</tr>
<tr>
<td>Cardiac syncope</td>
<td>Arrhythmia and/or structural heart disease leading to decreased cardiac</td>
<td>Arrhythmia:</td>
</tr>
<tr>
<td></td>
<td>output</td>
<td>- Bradyrhythmias (sinus node dysfunction), high grade type II AV block,</td>
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<tr>
<td></td>
<td></td>
<td>- Tachycardia-bradycardia syndrome</td>
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<tr>
<td></td>
<td></td>
<td>- Ventricular tachyarrhythmias</td>
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<tr>
<td></td>
<td></td>
<td>Structural heart disease:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Valvular heart disease</td>
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<tr>
<td></td>
<td></td>
<td>- Hypertrophic cardiomyopathy</td>
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<tr>
<td></td>
<td></td>
<td>- Atrial myxoma</td>
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</tbody>
</table>

### Approach to Syncope in the Emergency Room

#### Classification and Etiology of Syncope

Syncope can be classified into three broad groups:
- Reflex (neurally mediated), or vasovagal syncope
- Syncope due to orthostatic hypotension
- Cardiac syncope

In about one-third of cases the etiology of syncope is unexplained, while in 10–15% of patients the etiological diagnosis of syncope remains unclear even after thorough evaluation using current diagnostic guidelines. The different types of syncope, their underlying mechanism of development and common causes are outlined in Table 1.

#### Step-by-Step Approach in the Management of Syncope in the Emergency Room

Step-by-step approach in the management of syncope in the ER settings can be broadly sub-divided under the following headings (Box 1):

**BOX 1**

Step-by-step approach in management of syncope in the emergency room

- Confirmation of diagnosis of syncope by differentiating from other common causes
- Determination of the cause of syncope
- Risk assessment of syncope
- Management strategy based on risk profile

### Confirmation of Diagnosis of Syncope by Differentiating from Other Common Causes

Syncope occurs due to a transiently occurring global cerebral hypoperfusion. Since cerebral hypoperfusion cannot be clinically determined one has to depend on the clinical parameter of T-LOC for a diagnosis of syncope. But T-LOC can occur due to various causes other than syncope as already mentioned. Setting aside the traumatic causes of T-LOC from our current discussion, the various common non-traumatic causes of T-LOC (Table 2) should be brought into the differential diagnosis of syncope.
in any patient brought to the ER with T-LOC without any apparent cause. Some of the common causes from which syncope has to be frequently differentiated include seizures, hypoglycemia, narcolepsy with cataplexy, and certain psychiatric disorders.

### Syncope versus Seizures

Syncope and seizure are the two most common causes of T-LOC and differentiation between the two is not always as easy. Both generalized and partial seizures may be confused with syncope, although there are several differentiating points between the two. Similar to the tonic-clonic movements of generalized seizures involuntary movements like myoclonus may occur in up to 90% cases of syncope, along with mild flexor and extensor posturing. Likewise, partial or partial-complex seizures with secondary generalization are commonly preceded by an aura, which should be differentiated from the premonitory features of syncope. Further, autonomic manifestations of seizures like cardiovascular, urogenital, pupillary, and cutaneous manifestations may mimic the premonitory features of syncope; the arrhythmias associated with the cardiovascular manifestations may even lead to LOC. Nevertheless, the presence of accompanying non-autonomic auras may help differentiate these episodes in seizures from syncope. Among the points of differentiation between seizures and syncope, the LOC in seizures is usually more than 5 minutes duration with prolonged postictal drowsiness and disorientation, whereas in syncope the patient regains orientation almost immediately after the event. Muscle aches may occur after both syncope and seizures, but are more severe and long lasting after a seizure. Unlike syncope, seizures are rarely provoked by emotions or pain. Further, while incontinence of urine may occur with both seizures and syncope, fecal incontinence very rarely occurs with syncope.

### Syncope versus Hypoglycemia

Insulin induced hypoglycemia in diabetes mellitus may cause T-LOC, which is usually preceded by features of sympathetic overactivity like tremor, palpitations, anxiety, sweating, hunger, and paresthesia. Hunger is particularly not a typical premonitory feature of syncope. Additional neuroglycopenic features in hypoglycemia include fatigue, weakness, dizziness, and cognitive and behavioral symptoms, which are not found in syncope. Diagnostic difficulties of hypoglycemia may occur in those with strict glycemic control and repeated hypoglycemic episodes leading to blunting of the characteristic warning symptoms of hypoglycemia, or hypoglycemia unawareness.

### Syncope versus Cataplexy

Patients with cataplexy, which occurs in about two-thirds of patients with narcolepsy, experience an abrupt onset of partial or complete loss of muscular tone lasting for short durations of 30 seconds to 2 minutes; usually triggered by strong emotions like anger or laughter. Unlike syncope, consciousness is maintained throughout the attacks, and there are no premonitory symptoms.

### Syncope versus Common Psychiatric Ailments

Various psychiatric disorders like generalized anxiety, panic disorders, major depression, and somatization disorders are associated with an apparent LOC. These should be considered in individuals who faint frequently without prodromal symptoms. In such patients there is rarely any injury in spite of repeated falls; and there are no clinically significant hemodynamic changes like hypotension and bradycardia associated with these episodes which is found typically in vasovagal syncope.

### Determination of the Cause of Syncope

Once a diagnosis of syncope has been made in the ER and other likely causes of T-LOC have been clinically excluded, one should look for any serious underlying cause for the
syncope. In about 50% of cases the cause can be identified in the ER; the serious among them are usually some non-cardiovascular causes like a ruptured abdominal aortic aneurysm, an upper gastrointestinal bleeding or a subarachnoid hemorrhage. Underlying cardiovascular conditions especially arrhythmias are less frequently recognized in the ER unless it is present in the ECG on admission.

**Risk Assessment of Syncope**

When the cause of syncope cannot be ascertained in the ER, subsequent management should be guided by assessing the risk of a serious outcome in the future, especially a major cardiovascular event or sudden cardiac death. Such risk stratification includes determining the type of syncope and the patient's risk factors for a cardiac event.

There are three major types of syncope as described earlier (Table 1). Syncope, which is thought to be due to either reflex or postural cause, is likely to be at low risk of serious outcome. Patients with syncope of cardiac origin are usually at a higher risk of serious outcomes. The 2018 European Society of Cardiology (ESC) guidelines for the diagnosis and management of syncope provide a list of high-risk and low-risk features for risk stratification of syncope in the ER. These are based on certain clinical features of the syncopal attack, past history of the patient, and findings in the ECG.

**Management Strategy Based on Risk Profile**

Patients who have low-risk features are usually due to reflex or postural syncope. These patients usually have either some prodromal features or typical precipitating event(s). There may be a history of recurrent syncope, and the physical examination and ECG are usually normal. The outcome in patients with reflex syncope is usually very good. Syncope due to postural hypotension also has a low risk, but the prognosis is poorer than in reflex syncope due to their comorbidities. These patients can be usually discharged from the ER without hospitalization. Some patients with frequent episodes of syncope or syncope-related injuries are usually referred to special clinics for further evaluation.

Patients who have high-risk features usually do not have associated prodromal symptoms or typical precipitating events like in those with low-risk features. These patients also usually have history of structural heart diseases, and their physical examination and ECG findings are usually abnormal. Structural heart disease and primary arrhythmias are major risk factors for sudden cardiac death and overall mortality. These patients are candidates for further investigations such as echocardiography, ECG monitoring, and other sophisticated tests and referral to specialists. These patients should not be discharged from the ER and preferably hospitalized for specialist consultations and special tests mentioned.

**Clinical Evaluation in the Emergency Room Setup**

Some specific baseline investigations should be carried out in the ER setup. An ECG is important because a normal ECG practically rules out any cardiological cause of syncope, except for transient arrhythmia. First-degree heart block is neither associated with a cardiac nor reflex cause of syncope. An estimation of the random blood glucose should be done to exclude hypoglycemia, which may present as collapse or seizure. Estimation of hemoglobin and the hematocrit will exclude anemia, and blood loss as a cause of syncope. Blood tests for troponin and D-dimer should be done when myocardial ischemia-related syncope or pulmonary embolism is suspected. A chest X-ray or a CT brain is routinely not required.

**Special Tests and Investigations**

**Carotid Sinus Massage**

Carotid sinus massage (CSM) should be considered in patients over the age of 40 years with reflex syncope of unknown origin. In patients with history or clinical features of reflex syncope, if CSM causes symptomatic bradycardia and/or hypotension one can diagnose carotid sinus syndrome.

**Active Standing to Measure Postural Blood Pressure**

Postural hypotension is a progressive and sustained fall of more than 20 mm Hg of systolic or more than 10 mm Hg of diastolic blood pressure (BP) from baseline or a decrease in systolic BP to less than 90 mm Hg. In classic orthostatic hypotension the time from upright position to abnormal BP response is less than 3 minutes and in delayed orthostatic hypotension it is more than 3 minutes. It is important that the procedure should be done by the clinician and not delegated to other ER staff.
**ECG Recording**

In addition to the standard 12-lead ECG, the patient should be put on continuous ECG monitoring if cardiac arrhythmia is suspected to be the cause of the syncope. It has been found that ambulatory ECG monitoring in unexplained syncope can identify arrhythmia to be the cause for the syncope in about 10% patients with a diagnostic yield in about 75% of such cases.\(^\text{17}\)

**Echocardiography**

Patients with a heart murmur or history of structural heart disease requires an echocardiographic examination. One has to differentiate a benign flow murmur from a murmur of aortic stenosis and hypertrophic cardiomyopathy.\(^\text{18}\)

**Troponin to Rule Out Acute Coronary Syndrome**

Where ECG changes are consistent with acute myocardial ischemia high sensitivity troponin test should be done to rule out acute coronary syndrome.\(^\text{19}\)

**Decision Regarding Hospitalization**

Across the world the hospitalization rate of patients with syncope attending the emergency department is quite high. About one half of these patients attending the emergency department are usually hospitalized; and approximately half of the admitted patients would be discharged with no clear diagnosis, even after extensive investigations.\(^\text{20}\) Many of the hospitalizations for syncope are unnecessary; two-thirds of serious outcomes occur while the patient is in the ER and the rate of serious outcomes after the patient is shifted out of the ER is actually quite low, being as low as 3.6% at one-month follow-up.\(^\text{3}\) Hospitalization is indicated mainly for patients requiring syncope-related treatment and those with severe comorbidities or syncope-related injury caused by the primary event. In developed countries where there are specialized syncope clinics with facilities for investigations and treatment in the ER setups patients with higher risk profiles can be managed in the ER settings and so hospitalization can be rationalized.\(^\text{20,21}\) However, since such advanced syncope units are not commonly available in developing countries patients with high-risk should be ideally hospitalized for further evaluation and appropriate management.

**Conclusion**

Syncope is a common medical emergency. In the ER setting it is very important to first differentiate it from other serious causes of transient LOC like seizure or hypoglycemia. Thereafter, one should try to find out the underlying cause of syncope. A thorough history and clinical examination, and an ECG can most of the time distinguish the high-risk group of syncope due to heart diseases from those with lower risks due to orthostatic hypotension or reflex syncope. Additional tests like carotid sinus massage, echocardiography, cardiac troponin, or ECG monitoring may be required in the ER setting. Those with a high risk require urgent investigation and hospitalization.

**References**

Abstract

Nail, a cutaneous appendage, serves as an invaluable tool in unveiling the underlying systemic diseases. The nail changes can precede or coexist with the underlying systemic diseases. The presence of a particular nail change in several or all the nails is the feature of systemic disease or associated dermatologic disorder. The nail changes can involve various components of the nail such as nail matrix, nail plate, nail bed, or periungual tissue. In this chapter, we have discussed about various nail changes, specific features to identify them and its usefulness in delineating the associated systemic diseases comprehensively.

Introduction

Nail changes serve as window for diagnosis of several systemic diseases. Hippocrates in 5th century described clubbing to be associated with several systemic diseases. Since then several nail changes were found to be associated with systemic diseases. The nail changes in isolation or as a complement help to diagnose underlying disease. Nail changes can precede or can occur coexist with systemic disorders. Fingernail changes are more reliable than toenail changes since toenail changes can be altered by trauma. The components of nail unit is illustrated in Figure 1.

In this chapter, comprehensive facts regarding identification of nail changes and the systemic diseases associated with them are discussed. An important fact that needs to be emphasized upon is that trauma to the nail matrix or nail can result in several nail changes which will be confined to the trauma inflicted nail only. Whereas the nail changes due to the systemic diseases will be seen uniformly involving all the nails. The nail disorders that will be discussed are briefed in Table 1.

Koilonychia (Spoon-shaped Nails)

It is characterized by concave dorsal surface of the nail (Fig. 2). It is due to fragility of nails coupled with increased pressure exerted at the lateral and distal edges of the nails that make these edges to get reverted. The
central aspect is depressed since it’s tightly attached to nail bed. Koilonychia can be congenital, acquired, or idiopathic. Iron deficiency anemia is the most common systemic cause followed by hemochromatosis, Raynaud’s phenomenon, or systemic lupus erythematosus and among high altitude inhabitants. It can also develop due to trauma to the nail matrix area, occupational exposure to petroleum-based solvents.

**Beau’s Lines**

These are transverse lines or ridges, which are parallel to lunula of the nails (Fig. 3). They develop due to acute febrile illnesses, acute myocardial infarction, malnutrition, chemotherapeutic drugs, or trauma to nail matrix area. It occurs due to temporary cessation of nail growth. Nail grows at a rate of 3.5 mm per month approximately. Considering this fact, the distance of these lines from the cuticle tells about the time period before when the systemic disease had resulted. The width of the line tells about the duration of illness.

**Clubbing**

Clubbing refers to the nail change featured by increased longitudinal and transverse curvature of nail plate combined with soft tissue hypertrophy of the digital pulp usually seen involving all the nails (Fig. 4). Clubbing is extensively studied and it forms an integral component of general physical examination. Clubbing can be hereditary, acquired, or idiopathic.

The causes for clubbing can be remembered by the mnemonic CLUBBING which include:

- **Cardiac diseases:** congenital cyanotic heart diseases, acyanotic congenital heart diseases with reversal of shunt, infective endocarditis, atrial myxoma
- **Lung diseases:** lung abscess, bronchiectasis, emphysema, mesothelioma, cystic fibrosis, tuberculosis, pulmonary AV malformation, tuberculosis with cavitation

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**TABLE 1**

Classification of nail changes pertaining to systemic diseases

<table>
<thead>
<tr>
<th>Abnormalities of nail surface</th>
<th>Abnormalities of nail color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koilonychia</td>
<td>Leukonychia (total, striate, &amp; punctate)</td>
</tr>
<tr>
<td>Beau’s lines</td>
<td>Terry nails</td>
</tr>
<tr>
<td>Clubbing</td>
<td>Muehrcke’s lines</td>
</tr>
<tr>
<td>Pitting</td>
<td>Lindsay nail</td>
</tr>
<tr>
<td>Longitudinal ridging</td>
<td>Splinter hemorrhages</td>
</tr>
<tr>
<td>Pterygium</td>
<td>Melanonychia</td>
</tr>
<tr>
<td></td>
<td>Cyanosis</td>
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<tr>
<td></td>
<td>Icterus</td>
</tr>
<tr>
<td></td>
<td>Yellow nail syndrome</td>
</tr>
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<td></td>
<td>Nicotine staining</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormalities in nail attachment</th>
<th>Abnormalities in periungual region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onycholysis</td>
<td>Periungual telangiectasia</td>
</tr>
<tr>
<td>Pterygium</td>
<td>Paronychia</td>
</tr>
</tbody>
</table>

*Apparent leukonychia is due to the changes in the nail bed, which makes the nail look white
Ulcerative colitis & Chron’s disease (inflammatory bowel disease)

- Biliary cirrhosis (primary), cirrhosis due to other causes
- Bronchogenic carcinoma (most commonly small cell)
- Idiopathic
- Congenital
- Gastrointestinal: malabsorption (celiac disease)

Miscellaneous causes: HIV, sarcoidosis, Hodgkin’s disease, thyroid disorders, thymus tumor, and acromegaly.

Clubbing is caused by proliferation of connective tissue (fibroblasts, blood vessels, and bone tissue) and edema under the influence of VEGF (Vascular Endothelial Growth Factor) or PDGF (Platelet Derived Growth Factor) the levels of which get increased due to hypoxia or malignancies.

Unilateral and unidigital clubbing can be caused by several factors as mentioned in the Table 2.

There are three famous geometric forms associated with clubbing namely:

- Lovibond angle: It is the angle between the nail plate and the proximal nail fold. It is usually less than 160° but increases beyond 180° in clubbing.
- Curtis angle: It is the angle at the distal interphalangeal joint. Normally it is 180°. But in clubbing, it is reduced to less than 160°.
- Schamroth sign: It is featured by the obliteration of the diamond shaped space which is formed by approximation of the distal interphalangeal joint and the nail plate of the right and left identical digits.

Following are the grades of clubbing:

- Grade 1: Fluctuation of nail bed
- Grade 2: Increased anteroposterior and transverse diameter of nails
- Grade 3: Increase in pulp tissue resulting in drumstick appearance of the fingers
- Grade 4: Hypertrophic osteoarthropathy (HOA) characterized by deep pain in the distal extremities more during night and on dependency.

Onycholysis

It is characterized by detachment of nail plate from nail bed resulting in whitish or yellowish coloration (Fig. 5). This color change is due to the presence of air column beneath the detached portion of the nail plate. It can result due to numerous factors namely local causes (trauma, working in wet environment), cutaneous disorders (psoriasis,
onychomycosis), and systemic causes (hyperthyroidism). Onycholysis in hyperthyroidism is called “Plummer’s nails.”

**Pterygium**

It is the extension of the proximal nail fold over the surface of nail plate commonly seen in lichen planus (Fig. 6). Pterygium inversum is a condition in which the nail bed tissue is attached to the distal under surface (ventral surface) of the nail associated with obliteration of distal groove. It is commonly seen in scleroderma.

**Leukonychia**

It denotes the white coloration of the nails (Fig. 7). If the white color is due to abnormal keratinization it causes true leukonychia whereas the changes in nail bed lead to apparent leukonychia. Apparent leukonychia fades on application of pressure to the surface of the nails whereas true leukonychia remains unaltered. True leukonychia grows out along with the growth of the nail plate whereas apparent leukonychia persists since it is due to the changes in the nail bed.

**Total Leukonychia**

It is most commonly congenital or can develop secondary to renal failure, liver disorders, protein losing enteropathies, following acute illnesses.

**Punctate Leukonychia**

It is characterized by white dot or streak seen involving nail(s). It is caused by trauma to the nail plate or nail matrix, commonly due to nail biting or habitually picking the proximal nail fold.

**Mees’ Lines**

It is a classic example of striate true leukonychia, which is seen involving the whole width of the nails. They do not fade on application of pressure and they grow out with time. Though it is characteristically known to occur in Arsenic toxicity, it is also reported in carbon monoxide poisoning, congestive cardiac failure, renal failure, due to chemotherapeutic medications, Hodgkin’s disease, and pneumonia.

**Terry Nails**

It is featured by whitish (pale) proximal portion and normal vascular band distally. It is seen associated with congestive cardiac failure, adult-onset diabetes mellitus, peripheral vascular disease, hemodialysis, and HIV. Altered nail bed vascularity is a probable pathogenesis.

**Muehrcke’s Lines**

These are apparent leukonychia featured by paired white lines, which run parallel to the lunule most commonly seen on the 2nd, 3rd, and 4th fingernails. They fade on
application of pressure and they do not grow out with time. It is commonly caused by chronic hypoalbuminemia and chemotherapeutic medications (commonly by doxorubicin and cyclophosphamide). The localized edema of nail bed that compresses the vasculature is hypothesized as the pathogenesis.

**Half and Half Nail (Lindsay Nail)**

It is characterized by normal proximal half and brownish discoloration of distal half of the nail (Fig. 8) and is seen in patients with chronic renal failure. It is due to increased vascular proliferation in the distal nail bed.

**Splinter Hemorrhages**

These are tiny linear red or brown streak oriented linearly and longitudinally (Fig. 9). It occurs due to extravasation from subungual blood vessels. Its occurrence in many or all the nails indicates systemic cause. Subacute bacterial endocarditis is the most common systemic cause followed by SLE, antiphospholipid antibody syndrome, Raynaud’s disease, rheumatic heart disease, rheumatoid arthritis, internal malignancies, and medications (aspirin, warfarin, chemotherapeutic medications, tetracycline, and ganciclovir). Certain dermatologic diseases like psoriasis and lichen planus can also be associated with splinter hemorrhages.

**Melanonychia**

It is featured by black discoloration of the nail most commonly in the form of longitudinal black line (longitudinal melanonychia) (Fig. 10). It occurs due to trauma, racial factors, smoking, iron deficiency anemia, hemochromatosis, thyroid disease, Addison’s disease, HIV infection, and medications (antimalarials, minocycline, phenytoin, psoralens, sulfonamides, zidovudine, doxorubicin, methotrexate, and azathioprine). It can be due to melanoma, which is characterized by pigmentation.
of the proximal nail fold (Hutchinson sign), irregular black pigmentation of nail plate and wider band size.

**Nicotine Staining of Nails**
It is characterized by yellowish discoloration of the nails seen in chronic smokers.

**Cyanosis**
The bluish discoloration is due to the change in the color of the nail bed, which is seen through the nail plate. It is seen in the conditions causing peripheral cyanosis such as cold exposure, congestive cardiac failure, peripheral vascular disease. Transient cyanosis preceded by pallor and followed by erythema is the sequence of color change in Raynaud's phenomenon.

**Icterus**
In hyperbilirubinemia, the nails appear yellowish.

**Yellow Nail Syndrome**
It refers to the triad of yellowish color change of the nails, lymphedema and pleural effusion. It usually develops in the adults but can occasionally occur during childhood also.19

**Red Lunula**
It is seen in collagen vascular disorders, psoriasis, cardiac failure, cirrhosis, chronic obstructive pulmonary disease (COPD), and carbon monoxide poisoning.19

**Periungual Telangiectasia**
It serves as an important marker in the diagnosis of SLE, scleroderma, and dermatomyositis. It is also seen in diabetes mellitus, COPD, and rheumatoid arthritis.

**Paronychia**
It is the inflammation of the nail fold(s) (Fig. 11). Acute paronychia is commonly caused by staphylococcus, the presence of which needs ruling out diabetes. Chronic paronychia is seen commonly among those who use detergents over a long span of time.

**Psoriatic Nail Changes**
Psoriasis is considered as systemic disease nowadays due to its association with metabolic disorder. Coarse pitting, longitudinal ridging, salmon patch, oil drop sign, and subungual hyperkeratosis are some of the classical nail changes in psoriasis (Fig. 12). The presence of nail changes in a patient with psoriasis predicts increased chances of development of psoriatic arthritis, especially distal interphalangeal arthritis type.20

**Onychomycosis**
It is the fungal infection of the nail unit caused by dermatophytes or non-dermatophyte molds (Fig. 13). It can be of various colors such as white, yellow, gray, or black. Onychomycosis is of four types based on the portion of nail it affects namely:

![Fig. 11: Acute paronychia](image1)

![Fig. 12: Coarse nail pits in psoriasis](image2)
Distal subungual onychomycosis (common type) is often seen in those whose feet or hands remain moist for prolonged duration. In diabetics and immunocompromised individuals, it is thicker and resistant to therapy.

Proximal subungual onychomycosis is usually seen in immunocompromised individuals, superficial white, and total dystrophic type.

Pseudomonas Nail Infection

It causes greenish discoloration of the nails. It is seen commonly in whom the hands or feet remain wet for prolonged duration.

Acknowledgement: Journal of the American Academy of Dermatology for the figures.

Conclusion

Nails serve as an invaluable tool to diagnose the underlying systemic diseases and thus it is important to identify the nail changes. Nails can be easily examined and is a convenient diagnostic tool and thus the importance of including the nail changes as a part of general physical examination should always be emphasized.

References

CHAPTER 119

Anatomic Localization of Classical Neurological Symptoms

Uddalak Chakraborty, Avik Mukherjee, Jyotirmoy Pal

Abstract

Anatomical localization means the site of lesion responsible for a patient’s symptoms and signs. Neurological localization requires a comprehensive understanding of anatomy and physiology of the nervous system. The process of localization shall begin during history taking, may be refined during clinical examination, and shall be reassessed after relevant diagnostic studies. Despite the advent and use of modern neuroimaging, nothing can replace a clinician’s acumen to localize based on history and examination.

Introduction

“I believe a neurologist who can happily spend 3 days examining a patient for challenging anatomical localization will also be able to make a correct diagnosis within 3 minutes in acute stroke. The most important outcome of a neurological examination is anatomical localization.” Localization is derived from the Latin word locus which means site. The diagnostic exercise of determination of the site of nervous system affected by a disease process, from the signs and symptoms, is termed as localization in neurology.

Some authors argue that emphasis on anatomical localization over years has hindered the development of therapies in neurological diseases including epilepsy, migraine, Guillain-Barré syndrome, Parkinson’s disease, multiple sclerosis and ischemic stroke, etc. However, the diagnosis of idiopathic epilepsy, migraine, and Parkinson’s disease still remains clinical. Specialized neuroimaging may have complemented the clinical diagnosis, but can hardly replace it; there lies the importance of localization.

Common neurological symptoms can be localized by meticulous history taking and appropriate clinical examination, but sometimes one should be aware of false localizing signs or symptoms, which may misguide the clinician. In this chapter, we will try to localize lesions based on a few common neurological symptoms.

Weakness

Weakness is a characteristic and common motor neurodeficit, which may or may not be accompanied by other symptoms per se. First of all, true weakness should be differentiated from apparent weakness, either a vague feeling of tiredness or even malingering which may present like organic weakness. Proper clinical examination noting especially the distribution of weakness, any distractibility and a properly conducted Hoover’s test may differentiate between these. After identification of true weakness, it should be categorized into an upper motor neuron type (UMN) or lower motor neuron type (LMN) weakness, differentiating features of which are given in Table 1.

UMN weakness predominantly affects extensors of upper limbs and flexors of lower limbs.

Hemiparesis

Weakness of upper limb, trunk, and lower limb of one side of body is usually the commonest presentation of stroke.
Hemiplegia means complete loss of motor function on that side.

Hemiparesis is usually due to involvement of contralateral corticospinal tract (CST) from cerebral cortex to lower medulla or ipsilateral CST in case of a high-cervical cord lesion. Localization of hemiparesis is demonstrated in Table 2. CST with possible sites of lesion in hemiparesis has been shown in Figure 1.

Cruciate hemiparesis: Weakness of ipsilateral upper limb with contralateral lower limb weakness is termed as cruciate hemiparesis. The neuroanatomical explanation involves the complex somatotopic and anatomical segregation of the CSTs in the decussation at the lower medulla oblongata or cervicomedullary junction. At this level, the ventromedially located arm fibers decussate rostral to the leg fibers, and a lesion at this specific point can lead to this entity.3

False Localization in Hemiparesis

Kernohan’s Notch Syndrome (Fig. 2): A supratentorial lesion may lead to transtentorial herniation of the temporal lobe, with compression of the ipsilateral cerebral peduncle against the tentorial edge; since this is above the pyramidal decussation, this may lead to a contralateral hemiparesis. Occasionally, the hemiparesis may be ipsilateral to the side of lesion, and hence false-localizing; this occurs when the contralateral cerebral peduncle is compressed by the free edge of the tentorium.4

Monoparesis may be localized to cerebral cortex or subcortex due to selective involvement representing that particular limb.

Paraparesis

Weakness of both lower limbs may also be a common presenting symptom. We have to differentiate UMN and LMN type of lesions from history and clinical examination (Table 3).

<table>
<thead>
<tr>
<th>Site of lesion</th>
<th>Features</th>
</tr>
</thead>
</table>
| Cerebral lesion Complete hemiparesis: Involvement of same side of face (predominantly lower half) with ipsilateral hemiparesis can be commonly localized in the internal capsule. | **Contralateral cortex:** Distal pre­dominant distribution of mild to moderate weakness with seizures, loss of cortical sensations, agnosia, aphasia, etc.  
**Contralateral subcortical (corona radiata):** Faciobrachial weakness with aphasia, homonymous visual field defects.  
**Internal capsule:** Dense hemiplegia, hemianopia, hemianesthesia.2 |
| Brainstem | Cranial nerve palsy LMN type with contralateral hemiparesis—crossed hemiparesis  
Ipsilateral Horner’s syndrome due to involvement of sympathetic trunk. May also be seen in ipsilateral thalamic lesions.  
Ipsilateral hemiataxia due to involvement of cerebellum and its connections. |
| Cervical cord | Ipsilateral hemiparesis sparing face  
Ipsilateral loss of vibration and joint position sense with contralateral pain and temperature loss, usually one to two segments below the lesion (Brown-Sequard syndrome)  
LMN findings at the level of lesion. |

Paraparesis Weakness of both lower limbs may also be a common presenting symptom. We have to differentiate UMN and LMN type of lesions from history and clinical examination (Table 3).

Features suggestive of myelopathy include a definite level below which sensory modalities may be impaired/absent; LMN weakness at the level of lesion and UMN weakness below the level of lesion and bladder/bowel disturbance.

Patient may complain a girdle-like sensation suggestive of the sensory level of cord involvement. **False localization:** Compressive lower cervical or upper thoracic myelopathy may produce spastic paraparesis with a mid-thoracic girdle sensation.5

Cerebral cause of paraparesis may be accompanied by seizure, headache, etc. Cauda equina and conus medullaris may be differentiated based on symptoms as in Table 4.

Quadriparesis

Weakness of all four limbs; may be again categorized into UMN and LMN (Table 5).
Sensory Abnormalities

Positive symptoms: Tingling (pins and needles), burning, band like, itch, aching.

Negative symptoms: Numbness, difficulty in coordination of limbs in dark places or closure of eyes (Table 6).

Pattern of sensory abnormalities have been shown in Figure 3. Localization of sensory abnormalities are given in Table 7.

Incoordination

In a patient with gait imbalance, we have to rule out any nerve and muscle disorder, spinal cord or basal ganglia disorder.

Localization of ataxia has been discussed in Table 8.
TABLE 4  Cauda versus conus medullaris

<table>
<thead>
<tr>
<th></th>
<th>Cauda equina</th>
<th>Conus medullaris</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Severe, asymmetric, radicular</td>
<td>Less common</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>Asymmetric lower limbs, patchy</td>
<td>Symmetric saddle anesthesia</td>
</tr>
<tr>
<td>Motor loss</td>
<td>Asymmetric</td>
<td>Symmetric</td>
</tr>
<tr>
<td>Sphincter involvement</td>
<td>Less common and late</td>
<td>Common and early</td>
</tr>
</tbody>
</table>

TABLE 5  Possible localization of quadriparesis

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>Localization</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMN</td>
<td>Cervical cord</td>
<td>False localization: Thoracic sensory level, paresthesia, clumsiness, and atrophy of hands.</td>
</tr>
<tr>
<td></td>
<td>Brainstem</td>
<td>High cervical cord/foramen magnum: • Neck stiffness, suboccipital pain in C2 distribution. • Electric shock like sensation on flexion of neck. • Sequential weakness (Ehrlich’s phenomenon) • Downbeat nystagmus, cerebellar ataxia (foramen magnum) • Onion skin pattern of sensory loss of face</td>
</tr>
<tr>
<td></td>
<td>Brain (bihemispheric lesion)</td>
<td>Cranial neve palsies, Horner’s syndrome, Internuclear ophthalmoplegia</td>
</tr>
<tr>
<td>LMN</td>
<td>Anterior horn cells</td>
<td>Pure motor weakness, prominent wasting, distal&gt;proximal</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>False-localizing radiculopathy</td>
<td>Predominant proximal weakness with sensory symptoms.</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>Idiopathic Intracranial Hypertension and cerebral venous sinus thrombosis and may manifest as acral paresthesias, backache and radicular pain, and less often with motor deficits</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>Distal symmetric weakness with sensory impairment in glove and stocking distribution.</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>Predominant proximal pure motor weakness with diurnal variation, fatiguability.</td>
<td></td>
</tr>
<tr>
<td>Pure motor weakness without diurnal variation, fatiguability.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Speech Disorders

A communication disorder in the form of slurred speech, strained/effortful speech, monotonous low volume speech, word finding difficulty, comprehension difficulty, and naming problems should be recognized at first.7,8

Dysarthria as difficulty of articulation should be segregated from aphasia; if dysarthria present, it may be localized depending on the following types:
- **Spastic dysarthria**: Pseudobulbar/UMN involvement
- **Flaccid dysarthria**: LMN involvement

TABLE 6  Distribution of symptoms in reference to sensory and autonomic fibers

<table>
<thead>
<tr>
<th>Fibers</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small fibers</td>
<td>Burning, painful dysesthesia, autonomic dysfunction</td>
</tr>
<tr>
<td>Large fibers</td>
<td>Sense of imbalance, limb incoordination, tingling</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Postural dizziness, fainting, heat or cold intolerance, sphincter dysfunction</td>
</tr>
</tbody>
</table>
Monotonous, hypophonic speech: Extrapyramidal involvement

Clumping of syllables with undue separation: Cerebellar involvement

Localization of aphasia may be done as follows:
- Reduced fluency with difficulty in word finding and impaired repetition: Broca’s aphasia
- Comprehension difficulty in terms of word and sentences with impaired repetition: Wernicke’s aphasia
- Expressive and comprehension difficulty: Global aphasia
- Isolated repetition difficulty: Conduction aphasia
- Preserved repetition with execution/comprehension difficulty: Isolation/transcortical aphasia.

**Visual Loss**

First of all, one shall be able to differentiate between decreased ability to see things, double vision or loss of pieces of visual field.
Monocular visual loss is suggestive of lesion in the eye itself or optic nerve anterior to the optic chiasma.

Binocular visual loss is suggestive of bilateral optic nerve lesion or a chiasmal/retrochiasmal lesion. Visual loss correctable by pin hole/glasses: Refractive error.

Visual loss not correctable by pin hole: Opacity in ocular media/neurological illness.

**Color Vision**

Acquired disturbance of color vision is suggestive of optic neuropathy and maculopathy; color desaturation being one of the earliest manifestations of optic neuropathy.

Localization of visual loss has been shown in Table 9. Pattern of involvement of visual field and their respective localization has been shown in Figure 4.

**Headache**

Headache is one of the most common symptoms we come across in our day-to-day practice. The pain sensitive structures in the cranium which may give rise to headache are as follows:

- Scalp and aponeurosis
- Middle meningeal artery
- Dura mater and dural sinuses
- Falx cerebri
### Possible localization of visual loss

<table>
<thead>
<tr>
<th>Site of lesion</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular media</td>
<td>Eye pain, lacrimation, redness, no improvement in vision with pin hole</td>
</tr>
</tbody>
</table>
| Anterior visual pathway     | • Monocular vision loss  
• Central scotoma/altitudinal field defect in one eye  
• Impaired color vision  
• Orbit: Isolated optic neuropathy  
• Optic canal/intracranial site: Other cranial nerves may be involved (III, IV, VI)  
• Lesions close to optic chiasma: Junctional scotoma |
| Posterior visual pathway    | • Binocular visual loss  
• Homonymous/heteronymous hemianopia  
• Color vision may be impaired |
| Cortical defect             | • Ventral occipitotemporal defect:  
  – Visual agnosia, prosopagnosia, topographognosia  
• Dorsal occipito-temporal defect:  
  – Akinetopsia, Simultagnosia, optic ataxia, ocular motor apraxia |

**Fig. 4:** Localization of visual field loss
Proximal segments of the large pial arteries
- Cranial nerves V, VII, IX, and X
- Cervical nerves C1, C2, and C3

Headache may result due to inflammation, traction, compression, or malignant infiltration of these structures.

Primary involvement of these structures may give rise to primary headaches, which have little localizing value, while secondary involvement, for example, trauma, raised intracranial tension may give rise to secondary headaches.

In case of an extracranial structure as the source of headache, the site of pain is precise, for example, inflammation of extracranial artery in giant cell arteritis can be localized to the tender vessel.

Lesions of paranasal sinuses, teeth, eyes, upper cervical vertebrae have less sharp localization, but pain is referred in a regional distribution.

Infratentorial lesions tend to produce an occipitonal distribution of headache, while supratentorial lesions produce a frontotemporal headache.10

Among the primary headaches, cluster headache and trigeminal cephalgias have a periorbital location while migraine is usually unilateral and tension type headache is bilateral in distribution.

Conclusion

In this chapter, the authors have tried to give an overview of anatomical localization of a few classical neurological symptoms. Despite the recent advances in neuroimaging and electrodiagnostics, the importance and significance of anatomical localization is still indispensable, as it can guide the clinician to focus on a particular neuroanatomical substrate and even cut the need of unnecessary extensive investigations. We hope that this overview serves as a useful guide to the clinicians in day-to-day practice.

References

Abstract
Diaphragm is a musculofibrous structure separating thorax and abdomen. While unilateral diaphragmatic weakness is mainly secondary to inflammatory, infiltrative or traumatic etiologies; bilateral weakness mainly happens in systemic neurological or myopathic disorders. Unilateral weakness is usually asymptomatic. Abdominal paradox is a characteristic clinical sign of diaphragm weakness. Sniff test is a very important diagnostic test for assessment of unilateral weakness. Thorough history, meticulous examination, and appropriate investigations are of paramount importance to evaluate and plan for management.

Introduction
The term "Diaphragmatic dysfunction" is used to describe mainly three conditions—diaphragmatic eventration, weakness, and paralysis of diaphragm.1 Eventration can be defined as a persistent and permanent elevation of a part or all of the hemidiaphragm due to thinning.1 Diaphragmatic weakness may be described as a partial impairment of the strength of the muscles of diaphragm to produce and maintain adequate pressure required for ventilation. On the other hand, paralysis of the diaphragm is used to denote complete impairment of this capacity.2 Based on the etiology, this disorder can be unilateral or bilateral; permanent or temporary. Diaphragmatic flutter is another rare variety of diaphragm dysfunction which is characterized by repeated and variable cycles of regular and involuntary contractions of diaphragm. Features of diaphragmatic flutter are dyspnea, epigastric pulsations, and pain in the thoracoabdominal region.

Anatomical Considerations
Diaphragm is the musculofibrous structure, which separates the abdominal cavities from thoracic cavities. It is formed of a peripherally located muscular part and a non-contractile central fibrous portion, which is again divided into costal, sternal, and lumbar muscular groups. The muscular component of the diaphragm is composed of Type 1 (slow, fatigue resistant) and Type 2 (fast) fibers. Phrenic nerve, which originates from the 3rd, 4th, and 5th cervical nerves (C3, C4, and C5) almost exclusively provide the afferent neurological supply to diaphragm. Both the phrenic nerves descend anterior to the scalene muscles and then travel between the subclavian arteries and veins in the neck to enter into the thorax. The right phrenic nerve travels caudally anterior to the brachiocephalic trunk along the right atrium and finally enters the abdominal cavity. The left phrenic nerve travels along the left ventricle caudally and supplies the diaphragm.
Diaphragmatic thickness is variable with gradual tapering from anterior to posterior costal areas and from the costal insertions toward central tendon. Under normal situation, the diaphragm functions as a piston to generate flow as it descends in the thoracic cavity and displaces the contents of abdominal cavity caudally thereby causing elevation of the lower portion of thorax. The negative
intrathoracic pressure thus created results in an inflow of air from mouth to lung, thereby creating tidal volume.

**Etiology**

**Causes of unilateral diaphragm weakness:**
- **Infiltrative or compressive processes:** Goiter, pathological lymph nodes, mediastinal or pulmonary malignancy, cervical arthritis, and spondylosis.
- **Inflammatory disease:** Shingles, post-viral, mononeuritis, chronic inflammatory demyelinating polyneuropathy, parsonage—Turner syndrome.
- **Traumatic lesions:** Central venous cannulation, nerve blockade, heart/lung/liver transplant, neck/heart surgery, chiropractic manipulation.

**Central neurological disease:** Multiple sclerosis, stroke, rhizotomy.

**Idiopathic.**

The etiologies of diaphragmatic dysfunction are described in Table 1.

**Causes of bilateral diaphragm weakness:**
- **Neurological disease:** Multiple sclerosis, amyotrophic lateral sclerosis, medullary transection, Guillain-Barré syndrome, severe cervical spondylosis, poliomyelitis, chronic inflammatory demyelinating polyneuropathy.
- **Myopathy:** Malnutrition, dysthyroidism, muscular dystrophies, amyloidosis, corticosteroid use, post-viral critical illness/ventilator induced diaphragm dysfunction, disuse atrophy/inactivity.

**TABLE 1**

**Etiology of diaphragmatic dysfunction**

<table>
<thead>
<tr>
<th>Anatomical location of the lesion</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortex</td>
<td>Cerebrovascular accident (CVA)</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>Arnold-Chiari disease</td>
</tr>
<tr>
<td></td>
<td>Vascular accident</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Traumatic injury to the cord</td>
</tr>
<tr>
<td></td>
<td>Degenerative (severe spondylosis)</td>
</tr>
<tr>
<td>Central nervous system (CNS)</td>
<td>Multiple sclerosis (MS)</td>
</tr>
<tr>
<td>Motor neurons</td>
<td>Amyotrophic lateral sclerosis (ALS)</td>
</tr>
<tr>
<td></td>
<td>Post polio syndrome</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic neuropathy</td>
</tr>
<tr>
<td></td>
<td>Syringomyelia</td>
</tr>
<tr>
<td></td>
<td>Spinal muscular atrophy (SMA)</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>Traumatic injury to the plexus</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic (Obstetric procedures, anesthetic blockade, radiotherapy)</td>
</tr>
<tr>
<td>Phrenic</td>
<td>Compression/infiltration (mediastinal neoplasms)</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Guillain Barre syndrome infection—Pneumonias, Lyme disease, Herpes zoster, HIV infection</td>
</tr>
<tr>
<td></td>
<td>Amyotrophic neuralgia (Parsonage-turner syndrome)</td>
</tr>
<tr>
<td></td>
<td>Thoracic surgeries</td>
</tr>
<tr>
<td></td>
<td>Others (Hypothyroidism, Malnutrition, Diabetes, Benign thyroid hypertrophy, vasculitis, porphyria, Charcot-Marie-Tooth disease)</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Lung</td>
<td>Obstructive airway diseases (Asthma and COPD)</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>Lambert-Eaton syndrome</td>
</tr>
<tr>
<td></td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td></td>
<td>Botulism</td>
</tr>
<tr>
<td>Muscular</td>
<td>Steroid myopathy</td>
</tr>
<tr>
<td></td>
<td>Pompe disease</td>
</tr>
<tr>
<td></td>
<td>Myositis</td>
</tr>
<tr>
<td></td>
<td>Muscular dystrophies</td>
</tr>
<tr>
<td></td>
<td>Mechanical ventilation</td>
</tr>
</tbody>
</table>
Connective tissue disease: Dermatomyositis, mixed connective tissue disease, systemic lupus erythematosus/shrinking lung syndrome.
Idiopathic.
Sepsis.

Clinical Features

Unilateral diaphragmatic paralysis: Patients are usually asymptomatic but may have limited ability to exercise. They may also have dyspnea on exertion and in supine position. Symptoms are more severe in persons with obesity or with other comorbidities including cardiac and pulmonary pathology. They may also have symptoms of gastroesophageal reflux and nocturnal hypoventilation. It is often diagnosed as an incidental finding on chest skiagram as an isolated elevation of hemidiaphragm.

Clinical examination is rather nonspecific. On auscultation, decreased breath sounds are heard at the base of affected hemithorax. Reduced diaphragmatic excursion may be clinically detected by percussion of the lower rib cage at the end of expiration and inspiration respectively. Occasionally, paradoxical thoracoabdominal movement occurs during sleep.

Bilateral diaphragmatic paralysis: Patients may show dyspnea on lying down (orthopnea). Respiratory distress, which occurs sometimes during rest, may be exacerbated at the time of immersion in water. Most of the patients with this disorder present with sleep disorders and features of significant hypoventilation.

On clinical examination, cyanosis, superficial, and rapid respiration, bilaterally diminished breath sounds or abdominal paradox may be noted. In bilateral diaphragmatic paralysis, inspiration occurs due to contraction of the accessory muscles of respiration such as scalene and sternocleidomastoid along with external intercostals.

Abdominal paradox: The characteristic clinical sign of diaphragmatic dysfunction is abdominal paradox. During inspiration, when there is rib cage expansion, paradoxical inward movement of abdomen does occur. When accessory inspiratory muscles of the rib cage and neck contract as compensatory mechanism and lower pleural pressure, the flaccid diaphragm moves in a cephalad direction with inward movement of the abdomen. This abnormal breathing pattern is mainly seen in supine position. It is mostly seen in bilateral diaphragmatic paralysis and rarely occurs in unilateral cases. When abdominal paradox is seen in unilateral diaphragmatic paralysis, it indicates generalized respiratory muscles weakness. The mechanism of abdominal paradox has been described in Figures 1A to D.

Sniff Test

Fluoroscopy of diaphragm is very important to evaluate diaphragmatic function. The motion of the diaphragm is assessed by doing a rapid and short inspiratory effort through nostrils (also known as “Sniff test”). In normal persons, diaphragm will move caudally. In unilateral diaphragmatic paralysis, paradoxical (cephalad) movement is seen on the side of paralysis. There is no diagnostic value of this test in case of bilateral diaphragmatic paralysis. False negative results may be obtained due to sudden caudal motion of the paralyzed diaphragm at the onset of inspiration, which is misinterpreted as contraction. This phenomenon happens due to abrupt relaxation of abdominal muscles at the beginning of inspiration following active contraction at expiration. False positive results may be seen in about 6% cases.

Diagnosis

Diaphragmatic dysfunction is most often suspected after the incidental finding of an isolated elevation of hemidiaphragm on chest skiagram or during evaluation of unexplained dyspnea. Diagnosis is mainly based on imaging modalities including radiography, chest ultrasound, and fluoroscopy. Tests include:

Lung function test is often performed as a first-line investigation to quantify and assess the physiological impact of diaphragm weakness.

- In unilateral diaphragmatic weakness, functional residual volume (RV) and total lung capacity (TLC) are normally preserved. Vital capacity (VC) is mildly decreased to approximately 75% of predicted value and 10–20% further decrease is noted in supine position.
- In bilateral diaphragmatic weakness, VC usually reaches 50% of predicted values and 30–50% further decrease is noted in supine position. RV remains elevated and TLC can even get reduced.

Radiologic fluoroscopy (real time view) with sniff maneuver to depict paradoxical motion.
Ultrasound to look at the movement of the diaphragm and changes in the muscle thickness. It is noninvasive, simple, readily available, and widely used both in the research and clinical setting. It is used to assess Tdi (static measurement of diaphragm thickness) and TFdi (inspiratory diaphragm thickening fraction).

Sleep studies: Polysomnography with concomitant noninvasive ventilation may be considered routinely as this approach has both a therapeutic and diagnostic value. Sleep disordered breathing (SDB) can be seen both in unilateral and bilateral diaphragmatic weakness and it becomes more prominent with the progression of the disease. Early consideration of polysomnography is very important in such patients.

Cardiopulmonary exercise testing.

Chest X-ray: The common alternative causes of an elevated hemidiaphragm on imaging have been depicted in Table 2.

Maximum inspiratory mouth pressures.

**TABLE 2** Common alternative causes of an elevated hemidiaphragm on imaging

<table>
<thead>
<tr>
<th>'False' hemidiaphragm paralysis</th>
<th>Extra-diaphragmatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgagni hernia</td>
<td>Subphrenic abscess</td>
</tr>
<tr>
<td>Bochdalek hernia</td>
<td>Pulmonary or mediastinal mass</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Traumatic rupture</td>
<td>Ascites</td>
</tr>
<tr>
<td>Lung resection</td>
<td>Asymmetrical emphysema</td>
</tr>
<tr>
<td>Lipomas</td>
<td>Atelectasis</td>
</tr>
</tbody>
</table>

Stimulation of phrenic nerve in the neck by magnetic or electrical stimulation.

Transdiaphragmatic pressure measurement (measure of strength of diaphragm).

Electromyography (EMG), a test which records and evaluates electrical activity produced by skeletal muscles.
### TABLE 3
Comparison between unilateral and bilateral diaphragmatic paralysis

<table>
<thead>
<tr>
<th>Diagnostic tools and treatment</th>
<th>Unilateral diaphragmatic paralysis</th>
<th>Bilateral diaphragmatic paralysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>Neck or chest surgery, shoulder or neck pain, neck injury, neuromuscular disease, cervical spine manipulation</td>
<td>Neck or chest surgery, shoulder or neck pain, neck injury, neuromuscular disease, manipulation of the cervical spine</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Asymptomatic, exercise limitation, unexplained dyspnea, incidental radiographic finding</td>
<td>Exercise limitation, unexplained dyspnea, orthopnea, dyspnea at rest, dyspnea when bending, respiratory failure, prolonged mechanical ventilation, constitutional symptoms</td>
</tr>
<tr>
<td><strong>Examination</strong></td>
<td>No abdominal paradox</td>
<td>Abdominal paradox</td>
</tr>
<tr>
<td><strong>Laboratory tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital capacity (% of predicted value)</td>
<td>&gt;70</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Decline in supine vital capacity (%)</td>
<td>10–30</td>
<td>30–50</td>
</tr>
<tr>
<td>Fluoroscopy</td>
<td>Sniff test positive</td>
<td>Not helpful</td>
</tr>
<tr>
<td>Thickening of diaphragm on inspiration</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Complications</td>
<td>Ocasional hypoventilation during sleep, atelectasis</td>
<td>Frequent hypoventilation during sleep, pneumonia, atelectasis, respiratory failure</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation period for recovery (yr)</td>
<td>1.5–3</td>
<td>1.5–3</td>
</tr>
<tr>
<td>Treatment for coexisting conditions</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reversal of metabolic disturbance</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Noninvasive positive pressure ventilation (NIPPV)</td>
<td>Usually not indicated</td>
<td>Often indicated</td>
</tr>
<tr>
<td>Plication of diaphragm</td>
<td>May be helpful</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Phrenic pacing</td>
<td>No</td>
<td>Yes in patients with high spinal cord injury (SCI)</td>
</tr>
</tbody>
</table>

- **Arterial blood gas analysis:** Alteration of ABG is a late sign indicating severe functional impairment.
- **Computed tomography scan** of the abdomen, chest or both.
- **Magnetic resonance imaging (MRI)** to detect any pathology involving nerve roots or spinal column.

### Therapeutic Management
- Observation and supportive management
- Treatment of concurrent medical conditions
- Inspiratory muscle training (IMT)
- Noninvasive ventilatory support
- **Diaphragm pacemakers** can be used in case of functioning phrenic nerves such as patients with trauma to spinal cord or motor neuron disease
- Surgical procedure in the form of **diaphragmatic plication**
- **Tracheostomy and mechanical ventilation** in patients with a severe life threatening disease or in case of high cervical cord lesion causing quadriplegia

The comparison between unilateral and bilateral paralysis of diaphragm regarding the diagnosis and management has been described in **Table 3**. Diagnosis and therapeutic algorithm for unilateral and bilateral diaphragm weakness have been depicted in **Flowcharts 1 and 2**.
Flowchart 1: Diagnostic and therapeutic algorithm for unilateral diaphragm weakness

1. Elevated hemidiaphragm if seen on chest radiograph
   - Perform CT scan of neck and chest
   - Phrenic nerve palsy if suspected

2. Lung function testing
   - Vital capacity (VC) < 80% predicted and decrease vital capacity > 15% while lying supine OR Maximum inspiratory pressure (MIP) < 60%

3. Dynamic imaging, either
   - Ultrasound: TF < 20%
   - Paradoxical mvt on fluoroscopy

4. Sleep evaluation (Polysonomography)
   - CPAP or nocturnal ventilatory support if indicated

5. Diaphragm weakness most likely
   - Optimal management of associated comorbidities: Observation for 6–12 months + pulmonary rehabilitation

6. Unilateral phrenic stimulation
   - Pdi, tw < 10 cm H2O

7. Congenital anomaly
   - Pseudo-elevated hemidiaphragm

8. Diaphragm weakness unlikely

9. Address specific cause if identified
   - Persistent symptoms?
   - Functional limitation?
   - Surgical candidate?

10. Consider plication of diaphragm

CPAP, continuous positive airway pressure; CT, computed tomography; MIP, maximal inspiratory pressure; PSG, polysomnography; TF, thickening fraction of the diaphragm; VC, vital capacity
Flowchart 2: Diagnostic and therapeutic algorithm for bilateral diaphragm weakness

Unexplained dyspnea, respiratory failure, intolerance to exercise, etc. +/- concomitant neurological of muscular disease

- Bilateral weakness unlikely
  - No
  - Bilateral diaphragm weakness is most likely
    - No
    - Yes
      - Specific cause should be addressed
      - Upper level spinal injury
      - Persistent respiratory failure
      - Intact phrenic nerves

- No
  - No
  - Yes
    - Functional imaging
      - Yes
        - Ultrasound: TF<20%
        - No fluoroscopy
      - No
        - Polysomnography and arterial gas sampling
          - PaCO₂>45 mm Hg
          - MIP<60 cm H₂O/VC<50% predicted
          - Night SpO₂<90% for >5 min
          - Consider initiating NPPV

MIP, maximal inspiratory pressure; NPPV, noninvasive positive pressure ventilation; TF, thickening fraction of the diaphragm; VC, vital capacity
Conclusion

Diaphragmatic weakness has been seen to be associated with poor clinical outcome in most instances. A detailed evaluation is often needed to find out the exact origin, to assess and plan to manage its impact on symptoms, exercise capacity, and sleep homeostasis. Diagnosis of bilateral or unilateral diaphragmatic dysfunction and management may be challenging for the physician as this is relatively rare, associated with subtle clinical features and difficulties faced in establishing the exact anatomical location and physiological alterations. Diaphragmatic dysfunction is often underdiagnosed but should never be neglected because it can be a very good prognostic indicator and this is often associated with a poor quality of life. Referral to a higher center with experience and expertise in this disease and access to phrenic nerve stimulation or pacing, diaphragm ultrasound and surgical expertise in diaphragm plication should be considered, where necessary.

References

Abstract
Chest pain is one of the most common problems faced in the emergency room. The challenge is to develop a strategy to identify more serious pathology from non serious ones, found in majority of patients. Assessment of patient history, physical examination, 12 lead ECG, and cardiac biomarkers form the basis of assessment of chest pain. First and foremost serious life threatening causes of chest pain such as acute coronary syndrome, aortic dissection, pulmonary embolism, tension pneumothorax, and cardiac tamponade have to be ruled out. History of characteristics chest pain have to be taken as per the pneumonic SOCRATES (site, onset, character, radiation, aggravating and relieving factors and severity) helps to differentiate the different causes of chest pain, cardiac versus non cardiac. Subsequently, for acute coronary syndrome, a 12-lead ECG will help to differentiate STEMI from non STEMI. Further the cardiac biomarkers such as highly sensitive cardiac specific troponin will help to identify unstable angina from NSTEMI.

Introduction
Chest pain is one of most frequent causes of attending the emergency department. It is also one of the most difficult diagnostic challenges which presents in an emergency room.

The differential diagnosis of chest pain syndrome is broad and disparate including disease processes that range from non urgent to life threatening. Furthermore within the consideration of life threatening causes patients may be suffering from coronary causes as well as pulmonary embolism, aortic dissection, aortic rupture, pneumothorax or even esophageal rupture. There are many other diagnoses, which are much less critical but as widely as musculoskeletal pain, zoster, pleurisy, pneumonia, or gastroesophageal reflux.¹

Goals
- Early diagnosis of acute coronary syndrome (ACS).
- Recognition of other life threatening causes.
- Minimize cost and hospitalization in patient with chest pain of benign etiology.
- Diagnostic assessment and triage based on the following etiologies:
  - Myocardial ischemia
  - Other cardiopulmonary causes—pericardial diseases, aortic emergencies, pulmonary conditions
  - Non-cardiopulmonary causes

Differential Diagnosis
- **Cardiac:** Myocardial ischemia, pericarditis, aortic stenosis, hypertrophic obstructive cardiomyopathy (HOCM)
- **Vascular:** Acute aortic syndrome, pulmonary embolism, pulmonary hypertension
- **Pulmonary:** Pneumonia, pleuritis, pneumothorax
- **Gastrointestinal:** Esophageal reflux, esophageal spasm, esophageal rupture, peptic ulcer, gallbladder disease
CHAPTER 121
Approach to Chest Pain in Emergency

- Neuromuscular: Costochondritis, cervical disc disease, trauma, Herpes zoster
- Psychiatric conditions

Rule Out Deadly Causes
ACS, pericarditis, acute aortic syndrome, pulmonary embolism, pneumothorax, esophageal rupture.
These are the serious causes of chest pain not to be missed.

How to Approach a Patient of Chest Pain?

History
Evaluating clinicians should assess the quality, location, pattern, provoking and alleviating factors, associated symptoms, past medical history.

Quality of Pain
Angina pain of myocardial ischemia is described as tightness, squeezing, or heaviness. Whereas pain of pericarditis is described as sharp stabbing in nature.

Pericarditis of an infectious etiology causes simultaneous involvement of the adjoining pleura so patients experience pleuritic chest pain characterized by a localized sharp lancinating pain, which aggravates on inhalation, coughing. Pain of infectious pericarditis felt in shoulders and neck as central diaphragm attains sensory supply from phrenic nerve. However, a more lateral diaphragmatic movement may lead upper abdominal pain.

Involvement of pleura as in pneumothorax may produce pleuritic chest pain similar to infectious pericarditis.

Massive pulmonary embolism can present as heaviness.

Acute aortic dissection leads to excruciating ripping pain or “tearing” pain.

Epigastric burning pain like sensation suggests acid reflux or peptic ulcer disease. Esophageal spasm can be severe squeezing identical to angina. Gallbladder disease produces a colicky pain.

Musculoskeletal disorders produce an aching pain whereas herpes zoster produces a sharp burning pain.

Localization of Pain
Myocardial ischemia typically produces retrosternal discomfort with radiation to neck, jaw, shoulders, or arms. Inferior wall AMI typically produces substernal or epigastric discomfort.

Chest pain of pericarditis can mimic AMI but can radiate to trapezius, which does not occur with angina.

Chest pain due to myocardial ischemia is poorly localized and diffuse while pleuritic chest pain is localized.

Ascending and descending aortic dissection differ in their location of pain with anterior aortic dissection producing midline anterior chest pain and descending aortic dissection producing back pain.

Gastrointestinal conditions usually produce abdominal or epigastric discomfort exception being esophageal pain, which is retrosternal in location.

Chest pain of Herpes zoster has dermatomal distribution.

Pattern
Chest pain of myocardial ischemia develops over minutes and is precipitated by activity and relieved by rest. Pain of stable angina lasts for 2–10 minutes and subsides on rest whereas pain of unstable angina persists even on rest. In case of myocardial infarction pain lasts for more than 30 minutes.

Chest pain in pericarditis is episodic in nature. Chest pain in aortic dissection, pneumothorax is of sudden onset.

Pain of constant intensity over a prolonged period of time is more likely to represent peptic ulcer disease than myocardial ischemia.

Aggravating and Relieving Factors
Pain of myocardial ischemia is usually relieved by rest. However, one should be aware of the phenomenon of “warm up angina” in which pain seems to get relieved by continuing at same or greater level of exertion.

Administration of nitroglycerin may relieve both myocardial ischemia pain as well as pain produced by esophageal spasm.

Pain of musculoskeletal etiology changes in intensity with positional change of upper extremities and neck.

Pain of pericarditis worsened by supine position and relieved by sitting upright and leaning forward.

Pain due to gastroesophageal reflux may be exacerbated by alcohol, some foods or reclining position.

Worsening of pain with food suggestive of peptic ulcer disease or cholecystitis, which may be relieved by acid reducing therapies. However, in setting of a
severe coronary atherosclerosis redistribution of blood flow to splanchnic vasculature after eating can trigger postprandial angina.

**Associated Symptoms**
Symptoms associated with myocardial ischemia may include sweating, dyspnea, nausea, vomiting, and faintness.

Pulmonary embolism and pneumothorax should be considered in the background of sudden onset respiratory distress.

Hemoptysis usually points toward pneumonia. Blood tinged frothy sputum can be found in heart failure.

**Syncope should prompt consideration of hemodynamically unstable conditions in pulmonary embolism and aortic dissection.**

Although nausea and vomiting suggest a gastrointestinal disorder, these symptoms may occur in the setting of myocardial infarction, especially inferior wall AMI because of activation of vagal reflex.

Oesophageal rupture usually associated with forceful vomiting.

**Past Medical History**
Assess for risk factors of coronary atherosclerosis and venous thromboembolism.

History of connective tissue disorder such as Marfan’s syndrome should increase the suspicion of acute aortic syndrome or spontaneous pneumothorax.

**Physical Examination**

**General**
Patients with AMI often appear anxious, pale, cyanotic, or diaphoretic.

Patients with AMI may describe their pain by clenched fist against sternum termed as “levine’s sign.”

Often body habitus is helpful. Like patients with Marfan’s syndrome have young tall thin built.

**Vital Signs**
Tachycardia and hypotension are suggestive of hemodynamic instability should prompt a rapid survey for AMI, massive pulmonary embolism, pericarditis with tamponade, tension pneumothorax, acute aortic dissection.

Tachypnea and tachycardia with hypoxemia point toward a pulmonary cause.

**Cardiac**
Search for characteristic pattern of JVP in cardiac tamponade or right ventricular dysfunction.

S4 in case of myocardial ischemia and S3 in case of infarction can be found.

Murmur of mitral regurgitation is found in case of complications of AMI. Murmur of aortic dissection indicates complications of aortic dissection.

Pericardial friction rub suggests pericarditis.

**Pulmonary**
Decreased breath sound, hyper-resonant percussion note in case of pneumothorax or localized crepitation in pneumonia.

Esophageal rupture or "Boerhaave syndrome" is associated with subcutaneous emphysema and on being auscultated crackling sound is heard (Hamman's crunch).

**Abdominal**
Localized tenderness can be found in gastrointestinal conditions such as gallbladder stone or pancreatitis.

Abdominal findings such as hepatic congestion can be found in right ventricular dysfunction.

**Musculoskeletal**
Localized swelling, tenderness are useful clinical sign for costochondritis (Tietze's syndrome). Vesicular rash is found in the area of discomfort suggests Herpes zoster.

**Battery of Tests**

**ECG**
ECG is essential for identification of patients with ongoing ischemia as well as secondary cardiac complications of other disorders. ST segment elevation, ST segment depression, and symmetric T wave inversions are useful for detecting myocardial ischemia.\(^3\) Serial evaluation of ECG every 30–60 minutes is recommended in emergency for evaluation of suspected ACS.\(^3\)

Hyperventilation associated with panic disorder can also lead to nonspecific ST and T wave abnormalities.

Pulmonary embolism produces rightward shift of ECG axis manifesting as S wave in lead I, Q wave, and T wave in
Flowchart 1: How to approach a case of chest pain

ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; UA, unstable angina; CXR, chest X-ray; CT, computed tomography; UA, unstable angina; ECG, electrocardiographic; TEE, transesophageal echocardiography; AoD, aortic dissection; c/w, consistent; hx, history; NSTEMI, non–ST-segment myocardial infarction; PE, pulmonary embolism; MRI, magnetic resonance imaging; V/Q, ventilation-perfusion; STE, stimulated echo.
Clinical Medicine

lead III (S1Q3T3 pattern of acute cor pulmonale is classic, termed as McGinn-White sign).

ST elevation with diffuse lead involvement and PR segment depression distinguishes pericarditis from AMI.

CXR

CXR is most useful for detection of lung causes such as pneumonia, pneumothorax.

CXR findings commonly associated with pulmonary embolism include Hampton’s hump or Westermark sign or Palla’s sign.

CXR showing subcutaneous emphysema suggests “Boerhaave syndrome.”

Cardiac Biomarkers

Circulatory proteins released from damaged myocardial cells are indicative of myocardial injury. Initially biomarkers may be normal even in patients with STEMI.

Cardiac troponin [cardiac specific troponin T (cTnT)] and cardiac specific troponin I (cTnI) are preferred biomarkers over creatine kinase MB and should be repeated in 3–6 hours in suspected ACS patients.

Serial changes in cardiac troponin are useful in discriminating acute causes of myocardial injury from chronic elevation due to underlying structural heart disease or end stage renal disease.4

Assessment of D-dimer test to aid in exclusion of pulmonary embolism.

Both B-type natriuretic peptide (BNP) and N terminal pro BNP (NT-proBNP) is useful in diagnosis of heart failure.

Echocardiography

Patients with mechanical complications of MI or pericardial tamponade diagnosed easily with echocardiography.

Transesophageal echo is more sensitive of aortic dissection than transthoracic echo.

Provocative Tests

Exercise electrocardiography (“stress testing”) is used for patients with low to intermediate risk of ACS who have not revealed a specific cause of chest discomfort on initial evaluation.5

Patients with ongoing chest pain should not be subjected to these stress tests.

Recent Advances

CT angiography has emerged as a sensitive technique for detection of obstructive coronary disease particularly in proximal third of major epicardial coronary arteries.6

CECT is useful for detection focal areas of myocardial injury.3

CT angiography can be used for exclusion of aortic dissection, pericardial effusion, and pulmonary embolism.

Cardiac MRI is an emerging technique for structural and functional evaluation of heart. Gadolinium enhanced MRI can provide early detection of MI and can define areas of myocardial necrosis accurately.

Early myocardial perfusion imaging can be performed for evaluating patients with low or intermediate risk of ACS.7

Flowchart 1 depicts the approach towards chest pain in the emergency room.

Don’t Forget the Rare One

Takotsubo cardiomyopathy characterized by abrupt onset chest pain and shortness of breath, triggered by an emotionally stressful event. It mimics AMI because it is associated with ECG abnormalities and elevated cardiac biomarkers. But surprisingly coronary angiography is normal. It has predilection for women above 50 years.

Conclusion

Chest pain is one of the most common causes for admission to emergency departments. Emergency clinicians have a difficult task identifying, which patients to admit and which patients to discharge home.

Evaluation of acute chest pain in emergency is time consuming and expensive and often results in uncertain diagnosis.

A very small percentage of evaluated patients are eventually diagnosed with ACS. Most common diagnoses are gastrointestinal causes. Few of patients with chest discomfort discharged on the presumption of non-ischemic etiology from emergency are later deemed to have had a missed myocardial infarction.

So, rapid and precise identification, triage, and treatment of high-risk cardiopulmonary conditions are necessary, while low-risk patients can be safely observed with less intensive monitoring.
References

2. Approach to the Patient with Chest Pain, Marc S. Sabatine and Christopher P. Cannon, Braunwald’s Heart Disease.
Abstract
Anemia is the most common symptom present in most of the clinics of tropical country and it is usually a common symptom in females and during pregnancy! Anemia, which is a symptom and not a disease, is defined as a decrease in the circulating red blood cell mass to below age specific and gender specific limit. Evaluation for anemia is one of the most common clinical problems seen in the present hospital settings. The evaluation of anemia may be straightforward in an otherwise healthy individual with a single cause of anemia, but in many cases the cause is not readily apparent and multiple conditions may be contributing. The first step in diagnosis of anemia is detection with reliable and accurate tests, so that the important clue to underlying causes are not overlooked and patients are not subjected to unwanted laboratory tests.

Introduction
Anemia, which is a symptom and not a disease, is defined as a decrease in the circulating red blood cell mass to below age specific and gender specific limit. It is difficult to directly measure RBC mass, so the hematocrit or the hemoglobin level in the blood are usually used instead to indirectly estimate the value. Evaluation for anemia is one of the most common clinical problems seen in the present hospital settings. The evaluation of anemia may be straightforward in an otherwise healthy individual with a single cause of anemia, but in many cases the cause is not readily apparent and multiple conditions may be contributing.

In clinical practice, the use of proper standard method of history taking and clinical examination supported by laboratory investigations still form the best approach. There are many ways to classify anemia, but none of them is perfect. The approach to find the cause of anemia differs for different groups depending on sex, age, and race. It is important to reach the exact diagnosis of anemia to give the proper treatment. The common traditional ways to classify the anemia depend on
- Red cell morphology and indices
- Pathogenesis
- Clinical presentation of anemia

Classification Based on RBC Morphology and Indices
The classification of anemia based on the red cell predominantly depends on the mean corpuscular volume (MCV) of RBCs. On the basis of MCV the anemia is classified as:
- Microcytic hypochromic anemia (MCV: <80 fl)
- Normocytic normochromic anemia (MCV: 80–100 fl)
- Macrocytic anemia (MCV: >100 fl)
Classification Based on the Clinical Presentation

- Acute: Due to hemolysis or bleeding
- Chronic Anemia: Due to various chronic diseases or due to bone marrow suppression

Flowchart 1 shows different types of anemia.

Classification Based on Pathogenesis of Anemia

- **Inadequate production**: These disorders may be due to:
  - Nutritional deficiency (vitamin B12/folic acid deficiency, iron deficiency)
  - Stem cell disorders
  - Bone marrow infiltration
  - Defective bone marrow function of ineffective erythropoisis

- Excessive destruction of RBS (hemolysis)
- Bleeding—acute or chronic

**Microcytic Anemia (MCV <80 fL)**

Microcytic anemia is defined as the presence of small, often hypochromic, red blood cell in a general blood picture as depicted in Figure 1 (GBP and is characterized by a low MCV (<80 fL) (Flowchart 2). Iron deficiency anemia is the most common cause of microcytosis. Overall, 50% of anemia is attributable to iron deficiency and accounts for approximately 8,41,000 deaths annually worldwide.6,7

Other causes of microcytic anemia are—

- Anemia of chronic disease
- Thalassemia
- Lead poisoning
- Sideroblastic anemia

---

**Flowchart 1**: Lab diagnosis cell morphology and type of anemia
**Non-megaloblastic Macrocytic Anemia**

Causes of non-megaloblastic anemia are not related to defective DNA synthesis and it is characterized by the absence of megaloblasts and instead, the presence of large but mature red blood cells.

Causes of non megaloblastic macrocytosis includes—
- Chronic alcoholism
- Liver disease
- Hypothyroidism
- Renal diseases

**Table 1** and **Flowchart 3** show the different parameters to differentiate the discussed causes of microcytic anemia.

For megaloblastic macrocytic anemia refer **Figure 2**.
TABLE 1 Classification based on RBC morphology and indices

<table>
<thead>
<tr>
<th>Parameters</th>
<th>IDA</th>
<th>BT</th>
<th>Lead poisoning</th>
<th>SA</th>
<th>CI</th>
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<td>MCV</td>
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<td>MCV: RBC (mentzer index)</td>
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</table>

BT, beta thalassemia; CI, chronic inflammation or infection; IDA, iron deficiency anemia; N, normal; SA, sideroblastic anemia

Flowchart 3: Lab diagnosis and cell morphology

Adult with microcytosis (mean muscular volume 80 fL)
- Check ferritin level
  - Ferritin level <15 ng per m:
    - Iron deficiency anemia
  - Ferritin level normal to high:
    - Check serum iron level, TIBC, and transferrin saturation
      - Serum iron level decreased:
        - TIBC decreased:
          - Transferrin saturation-decreased:
            - Suggests anemia of chronic disease
              - Normal hemoglobin A2 level
                - Sideroblastic anemia
                  - alpha-beta-thalassemia trait
                - Look for other hemoglobinopathies
      - TIBC normal transferrin saturation normal to increased:
        - Perform hemoglobin electrophoresis (consider earlier in the evaluation of children and young adults)
          - Increased hemoglobin A2 level
            - Look for other hemoglobinopathies
- Reticulocytosis
- Blood disorders like red-cell aplasia, aplastic anemia, myelodysplastic syndromes, and myeloid leukemia, PNH
- Drugs such as azathioprine
- Pregnancy

**Normocytic Anemia (MCV 80–100 fL)**

A mild normochromic, normocytic anemia is a frequent finding and mostly due to a consequence of other diseases, including:

- anemia of chronic disorders associated with chronic infection, malignant disease, all forms of inflammatory
diseases. The exact mechanism is unknown, but likely to involve multiple factors, which leads to a reduction in the serum iron concentration along with concurrent reduction in the level of transferring. That’s why saturation of the iron binding capacity is usually normal or only slightly reduced.

- Other disorders including renal failure, hypothyroidism, marrow failure (aplastic anemia, pure red-cell aplasia, infiltration), acute blood loss (Flowchart 4).8,9

**Conclusion**

A good clinician diagnoses the type of anemia but an excellent clinician always tries to search out the cause of the disorder. So, to manage a patient of anemia, every effort should be given in searching the etiology of anemia. The first step in diagnosis of anemia is detection with reliable and accurate tests, so that the important clue to underlying causes are not overlooked and patients are not subjected to unwanted laboratory tests.

**References**

Abstract
Aphasia refers to a disorder of language processing caused by a dysfunction in specific regions of the brain. It is common after stroke and associated with relevant disability and higher mortality. Evaluation of language function (spontaneous speech, auditory comprehension, naming, repetition, reading, and writing) allows classification of aphasia. Most patients present some degree of recovery. Speech and language therapy is an effective treatment for aphasia following stroke. Other approaches, e.g., pharmacotherapy, transcranial magnetic stimulation, are being investigated.

Introduction
While assessing a patient in a neurological ward or outpatient department, one has to frequently come across cases with communication disorders. It is important to distinguish among different types of communication problems which may range from language disorder to speech production at different levels.

Broadly, communication disorders are divided into two basic groups:
- Speech defect: consisting of Dysarthria and Dysphonia
- Language dysfunction: consisting of Dysphasia/Aphasia

The fundamental difference between a speech defect and aphasia remains as follows: if one transcribes the patient’s verbal expression into writing, it will read as combination of normal and grammatically correct sentences in speech defect which is not the case for aphasic participants. Thus, a language defect can simply be considered a more fundamental disturbance in communication machinery, which hinders appropriate expression of thoughts by any means, whereas in speech disorders thoughts can be properly expressed by the agency of nonverbal ways of communication, for instance writing (Fig. 1).

- Dysarthria: It is a disorder of the motor production or articulation of speech mainly of neurologic origin.
- Dysphonia: It is a term that describes voice disorders, for example, involuntary tightening or constriction of vocal cords causing interruptions of speech and voice quality.
- Aphasia/Dysphasia: It is an acquired disorder with loss or defective language content of speech resulting from damage to speech centers of dominant hemisphere (usually left in 97%).

Language has two parts:
- Expression
- Understanding

Expression
Expression has got three components:
- Emotional component: This component of expression does not require any learning and is an expression of inner suppressed emotions
Automatic component: This component of expression occurs automatically and is generally acquired through learning

Proposition: This is the actual speech component

Understanding
This occurs through a series of steps (Flowchart 1).

Examination
Examination of speech consists of testing of the following components:
- Spontaneous speech
- Comprehension (auditory)
- Naming
- Repetition
- Writing
- Reading

Spontaneous Speech
Generally motor speech defect (damage of Broca’s area) manifests as loss of spontaneous speech.
- Types:
  - Complete loss: Mutism (no speech)
  - Incomplete Broca’s area damage: This manifests in four forms (Flowchart 2):
    - MONOPHASIA: Repetition of the same word
    - PARAPHASIA: Single letter of a word or the entire word is substituted with similar sounding words

Example 1: “Tarun” → “Arun” : single letter substitution
Example 2: “Harry” is a bad boy. → “Tom” is a bad boy : entire word substitution
- NEOLOGISMS: New words without any meaning
- CIRCUMLOCUTION: The patient can name an object but uses different descriptions to describe a particular object
  Example: A cell phone when put in front of the patient, he can’t name the object but says “this is an object used to call someone”

Tests for Spontaneous Speech
- Fluency: Normal fluency is 100–150 words per minute or more than 7 words in a sentence, while non-fluency refers to less than 10–15 words per minute
- Pronunciation
- Capability of words/sentence formation
- Speech disorder like paraphasia

Comprehension
The patient’s responses to verbal requests and commands and to everyday questions and comments give information about his ability to understand speech.
Comprehension may be tested by having the patient follow verbal commands (“show me your teeth”, “stick out your tongue”). Comprehension can be judged to be reasonably intact if the patient follows a complicated multistep command. However, failure to follow a command does not necessarily prove that comprehension is impaired. A patient may not comply because of apraxia. Patients with left hemisphere lesion may even have apraxia for functions of their nonparietic left hand. When the patient does not follow simple commands, establish whether he can say or shake his head yes or no.

**Naming**

Some caution is necessary while testing for naming, as there are influences of age, culture, and education.

Naming is the function of parietal lobe.

**Test for Naming**

While testing naming, always use common object. Naming is said to be intact when patient is given several objects to identify and can name 12 items in 1 minute.

If the patient says less than 12 items, there are three possibilities:
- Can’t say name
- Can recognize the item, but can’t say the function
- Can say only 4 out of 12 items

**Repetition**

Repetition is the function of lower parietal lobe (arcuate fibers). The ability to repeat may be selectively involved or paradoxically preserved in certain aphasic syndromes. A patient’s repetition span (i.e., the number of words he can repeat) is usually two more than his digit span.

Types of repetition disorders include:
- Can’t repeat
- Can repeat only a part
- Can substitute with a new syllable or word
  - Repetition is preserved in anomic, transcortical, and some cases of subcortical aphasia.

**Writing**

**Pathway of Writing**

The patient’s ability to use written language should also be assessed. It may be disturbed in conjunction with abnormalities of spoken language, or separately. Patients who are aphasic in speech are also aphasic in writing, but writing may be preserved in patients with dysarthria or verbal apraxia. The ability to write to dictation is analogous to the ability to repeat verbal material. Copying written material also assesses the ability to transfer information from visual system to language area. Having the patient copy written material may also test the connections between the receptive language areas and Exner’s writing center (**Flowchart 3**).

**Reading**

The patient’s ability to comprehend written language symbols can be tested by having him read. Written language is perceived by the visual system and the information is conveyed to the perisylvian language centers. Dysfunctions of the language centers or interruption of the connections with visual system may cause inability to read (alexia).

**Pathway of Reading**

Visual association area → Angular gyrus

**Alexia (Fig. 2)**

- Alexia with lesion in Wernicke’s area: Reading and understanding impaired, can’t write dictation.
- Alexia without lesion in Wernicke’s area: Reading impaired but auditory understanding preserved. This is called PURE WORD BLINDNESS.
Types of Aphasia

- **Sylvian aphasia**: repetition will be lost
  - Broca’s aphasia
  - Wernicke’s aphasia
  - Conduction aphasia
  - Global aphasia
- **Perisylvian aphasia**: repetition is preserved
  - Anomic aphasia
  - Transcortical aphasia
  - Subcortical aphasia
  - Mixed aphasia

### Sylvian Aphasia (Table 1)

#### Broca’s Aphasia

- Fluency lost, patient will be frustrated but aware
- Communicate with small sentences with few words and with gestures
- Reading will be lost
- Writing preserved
- If there is combined damage of Broca’s area and Exner’s area, then both reading and writing will be lost
- **Associated** with corticospinal tract sign (Faciobrachial)

#### Wernicke’s Aphasia

- Lesion involves:
  - Angular gyrus
  - Supramarginal gyrus
  - Wernicke’s area
- Characteristics:
  - Damage to Auditory Association Area—**WORD DEAFNESS**
  - Damage to Angular Gyrus—**WORD BLINDNESS**
  - Fluency preserved
  - No appropriate response to any command (increased spoken words—**HYPERLABIA**)
  - Repetition lost

#### Conduction Aphasia

- Lesion involves the Arcuate fibers
- Characteristics:
  - Repetition lost
  - Fluency preserved
  - Comprehension is unaffected
  - Reading is lost
  - Writing is lost

#### Global Aphasia

- Features of above three aphasias
- **Associated** with hemianopia, hemisensory loss, hemiparesis

#### Perisylvian Aphasia

- **Anomic Aphasia**
  - Naming difficulty
  - All other modalities preserved
  - **Circumlocution** will be present

- **Subcortical Aphasia**
  - Repetition preserved
  - Lesion involves:
    - **Caudate nucleus**: Features of Broca’s aphasia with preserved repetition
    - **Thalamus**: Features like Wernicke’s aphasia with preserved repetition
**Transcortical Aphasia**

This is of two types (Fig. 3):
- **Transcortical sensory aphasia:**
  - Features like that of Wernicke’s aphasia with preserved repetition
  - Lesion involves the area posterior to central sulcus
- **Transcortical motor aphasia:**
  - Features like that of Broca’s aphasia
  - Lesion involves the area anterior to the central sulcus

**Anatomy of Speech Areas**

The classical model proposed by Wernicke consists of the following parts (Fig. 4):
- Primary auditory area
- Secondary auditory area
- Wernicke’s area (Sensory speech area)
- Broca’s area (Motor speech area)
- Arcuate fasciculus
- Primary visual cortex
- Primary somatic sensory cortex
- Primary motor cortex
- Angular gyrus
- Exner’s area

However, this classical model has been expanded and modified by recent reviews and are now part of **Dual Stream Model of Hickok and Poeppel.** Some of its components include:
- **Spoken speech processing:** Heschl’s gyrus (bilateral superior temporal gyrus)
- **Decoding of sounds into language information:** Wernicke’s area (area 22), in left superior temporal gyrus in its posterior part, as well as posterior parts of middle and inferior temporal gyri.
- **Phoneme processing:** Inferior parietal lobule, especially the supramarginal gyrus.
- **Reading comprehension:** Parieto-occipital cortex, especially the angular gyrus.
- **Spontaneous speech output:** Broca’s area in the posterior inferior frontal gyrus (areas 44, 45), and the premotor cortex which program the motor cortex to produce sounds.
- **Speech repetition:** Communication between the posterior and anterior speech regions via the arcuate fasciculus and uncinate fasciculus.
- **Alerting the language network:** Anterior thalamus, basal ganglia.

**Auditory Pathway and Speech**

The auditory pathway conveys the special sense of hearing. Information travels from the receptors in the Organ of Corti of the inner ear (cochlear hair cells) to the central nervous system carried by the vestibulocochlear nerve.

This pathway ultimately reaches the primary auditory cortex for conscious perception. In addition, unconscious processing of auditory information occurs in parallel (Figs. 5 and 6).
Aphasia

Aphasia as mentioned earlier is a loss or impairment of language production and/or comprehension, often accompanied by a loss of ability to read and/or write resulting from damage to speech centers within the dominant (usually left in 97%) hemisphere (Fig. 7).

A language disturbance occurring after a right hemisphere lesion in a right-handed person is known as Crossed aphasia.

Aphasia can be categorized according to whether the speech output is fluent or nonfluent:

- **Fluent aphasia (receptive aphasia):** It is the impairment mostly due to the input or reception of language with difficulties either in auditory verbal comprehension or in the repetition of words, phrases, or sentences spoken by others. For example, Wernicke’s aphasia.

- **Nonfluent aphasia (receptive aphasia):** These are difficulties in articulating with relatively good auditory, verbal comprehension. For example, Broca’s aphasia.

**Normal fluency:** Between 100–150 words/min, sentence length >7 words.
## TABLE 2  Domains of speech

<table>
<thead>
<tr>
<th>Domains</th>
<th>Methodology</th>
<th>Observations</th>
</tr>
</thead>
</table>
| **Spontaneous speech** | • Observe the speech and language during routine conversation  
• Ask open ended questions. Example:  
  − Why have you come to the hospital?  
  − Describe the nature of your job  
• If the patient is not communicative try recitation list. Example:  
  − List the days of a week  
  − List the months of the year | • Initiation difficulty  
• Articulation  
• Fluency  
• Prosody (the melodic intonation)  
• Grammatical correctness (agrammatic speech sounds like telegraphic language)  
• Paraphasias: 1 If present, literal2 or semantic3?  
• Neologisms4  
• Word finding pauses, circumlocution |
| **Naming**         | Show different categories like objects, body parts, colors, pictures of animals  
Example: pen, watch, key hand, thumb, dog, cat, red/blue/ yellow colors, names of familiar people | • Impaired naming, in spite of recognition of the object or the person  
• Impaired naming restricted to certain category  
• Confabulation  
• Word finding difficulty, pauses, circumlocution |
| **Auditory comprehension** | • One step commands (beware of apraxias)  
  − Stick out your tongue  
  − Point to your nose  
  − Open your mouth  
• Two steps commands (beware of body part agnosias, right left disorientation)  
  − With your right hand, point to your left ear  
  − Point to the ceiling and then to the floor  
  − Raise your hand and close your eyes  
• Yes or no responses (inform that patient should say yes or no)  
  − Is your name xxx? (use a wrong name)  
  − Is your name zzz? (use correct name)  
  − Do you live in xxx? (use wrong place)  
  − Do you live in zzz? (use correct place)  
  − Does Sunday come after Saturday? | • Impaired comprehension to spoken commands  
If apraxia/body part agnosia interferes with body part commands, impaired “yes/no” responses |
## Interpretation of Language Assessment

<table>
<thead>
<tr>
<th>Domain</th>
<th>Methodology</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Repetition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Single words:</td>
<td>• Impaired for difficult consonants in dysarthria</td>
</tr>
<tr>
<td></td>
<td>– Brown</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Chair</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Five hundred and fifty-five</td>
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<tr>
<td></td>
<td>• Sentence repetition (there should be no errors of omission or commission)</td>
<td></td>
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<tr>
<td></td>
<td>– It is 4 o’clock</td>
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<tr>
<td></td>
<td>– He locked the doors</td>
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<tr>
<td></td>
<td>– He searched for keys in his pocket</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– No ifs, ands, or buts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– He opened the sports page of the newspaper for cricket score</td>
<td></td>
</tr>
<tr>
<td><strong>Reading</strong></td>
<td></td>
<td>• Impaired letter formation</td>
</tr>
<tr>
<td></td>
<td>• Simple letters and words:</td>
<td>• Spelling errors (most useful in mild Wernicke’s aphasia)</td>
</tr>
<tr>
<td></td>
<td>– Alphabets (G, C, K, M)</td>
<td>• Impaired grammar</td>
</tr>
<tr>
<td></td>
<td>– Numbers (3, 8, 6, 9)</td>
<td>• Impaired reading comprehension, in spite of good speech comprehension in Broca’s aphasia</td>
</tr>
<tr>
<td></td>
<td>– Simple words (ear, ant, car, etc.)</td>
<td>• Relatively preserved reading comprehension in spite of impaired auditory comprehension in Wernicke’s aphasia</td>
</tr>
<tr>
<td></td>
<td>• Obeying written commands (carry cards with these commands written)</td>
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<tr>
<td></td>
<td>– Make a fist</td>
<td></td>
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<tr>
<td></td>
<td>– Open your mouth</td>
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<tr>
<td></td>
<td>– Point to the floor then point to the ceiling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– With your right hand point to the left knee</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Reading aloud with comprehension</td>
<td></td>
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<tr>
<td></td>
<td>– Ask patient to read a newspaper item and ask him relevant questions</td>
<td></td>
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<tr>
<td><strong>Writing</strong></td>
<td></td>
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<tr>
<td></td>
<td>• Ask patient to write few sentences about why he has come to the hospital</td>
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<tr>
<td></td>
<td>• Ask him to write about his job/business</td>
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<td></td>
<td>• Show him a picture and ask him to write a few sentences about it</td>
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<tr>
<td></td>
<td>• If the patient has right sided hemiparesis, ask him to use left hand</td>
<td></td>
</tr>
</tbody>
</table>

1. **Paraphasia**: It is a phenomenon of substitutions in speech components.
2. **Literal Paraphasia** (Substitution of one phoneme for another; e.g., foon for spoon)
3. **Semantic Paraphasia** (Substitution of one word for another; e.g., pan for spoon)
4. **Neologisms**: Use of non-existent words

### TABLE 3

<table>
<thead>
<tr>
<th>Aphasia</th>
<th>Site of lesion</th>
<th>C</th>
<th>R</th>
<th>F</th>
<th>Reading</th>
<th>Writing</th>
<th>Associated signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wernicke’s-sensory/receptive/posterior</td>
<td>Involvement of inferior division of middle cerebral artery</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Impaired, but sometimes relatively preserved (opposite of Broca’s aphasia)</td>
<td>Impaired, good letter formation, spelling errors, and poor grammars</td>
<td>Visual field defect</td>
</tr>
<tr>
<td>Broca’s-motor/expressive/anterior</td>
<td>Involvement of superior frontal branch of middle cerebral artery</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Impaired with preserved speech comprehension, especially for syntax (“third alexia”)</td>
<td>Impaired with poor letter formation and poor grammar</td>
<td>Right sided hemiparesis, apraxia of left limbs</td>
</tr>
</tbody>
</table>

*Contd...*
Contd...

<table>
<thead>
<tr>
<th>Aphasia</th>
<th>Site of lesion</th>
</tr>
</thead>
</table>
| Transcortical motor aphasia | • Left frontal lobe anterior to Broca's area  
• Frontal deep white matter  
• Medial frontal region neat SMA (in the anterior cerebral artery territory) |
| Transcortical sensory aphasia | Left temporo-occipital region |
| Transcortical mixed aphasia | Large watershed infarctions in the left hemisphere, sparing the perisylvian cortex, but disconnecting them from other cortical regions |
| Conduction aphasia | Lesion involving either the arcuate fasciculus or the superior temporal gyrus or the inferior parietal region (supramarginal gyrus) |
| Wernicke's aphasia | Lesion involving Wernicke's area and adjacent temporoparietal region (inferior parietal lobe, superior temporal gyrus) |
| Single word comprehension defect | Lesion limited to Wernicke's area |
| Broca's aphasia | Lesion involving the Broca's area and adjacent cortex and subcortical white matter |
| Isolated speech initiation defect | Lesion limited Broca's area |
| Global aphasia | Large lesion involving the left frontal, temporal, and parietal lobes |
| Anomic aphasia | Non-localizing left hemispheric disease. Usually superior temporal gyrus, but also frontal or parietal lobe near angular gyrus |
| Alexia with agraphia | Left angular gyrus lesions |
| Alexia without agraphia | Disconnection (of language areas from right occipital cortex) by splenial lesion plus left occipital lesion. Patient has intact left hemifield, but written information presented in that hemifield is not conveyed from right occipital cortex to the language areas |
| Third alexia | Impaired reading comprehension in Broca's aphasia |
| Speech alexia | Left frontal or insular lesion |
Approach to Aphasia

CHAPTER 123

Domains of Language (Table 2)

Language has to be assessed in six domains, which are as follows:

- Spontaneous speech
- Naming
- Auditory comprehension
- Repetition
- Reading
- Writing

Interpretation of Language Assessment

See Table 3.

Lesion Localization

See Table 4.

Conclusion

A social approach of language assessment that prioritizes subjectivity is possible when we use a fourth-generation method (Campos and Furtado, 2011), which goes beyond individual evaluation and rehabilitation, providing a more effective improvement. The plasticity of the human brain and training-induced learning improve the quality-of-life due to interference in the process of cognition of individuals with dysgraphia. Although their learning tends to be specific to the trained function and not transferred to similar tasks, there are no obstacles that prevent the discussion of new training schemes. These trainings can lead to the acquisition of new knowledge and to the development of new strategies so that they are used flexibly in various tasks and contexts. These challenges are responsible for increasing learning, for progressing the task difficulty, for the motivational state of the individual, and also for reflecting on the type of feedback that the training provides.

Suggested Readings
