INTRODUCTION

There are many references to delirium in the extant works of Hippocrates and thus its history goes back almost 2,500 years. Greek and Roman writers recognized three main forms of mental disorders: mania, melancholia, and phrenitis or delirium. Aretaeus, a second century Roman writer, classified diseases as acute or chronic, and phrenitis and lethargy (lethargus) were the chief acute mental disorders. While phrenitis typically involved restlessness, insomnia, and hallucinations, lethargy involved undue quietness and sleepiness. Both were believed to be caused by fever or poisons. Their treatment included both a physiological and a psychological approach [1].

The word delirium is derived from the Latin term for “off the track.” The term “delirium” was first used by Cornelius Celsus in the first century A.D., but on the whole the word “phrenitis” was used more often in the ancient medical literature. The first description of delirium in the English medical literature appeared in Barrough’s textbook The Method of Physick, first published in 1583 (Barrough, 1583). He referred to it as “frenesie” and observed that it involved the derangement of four main functions: imagination, cogitation, memory, and reason. It also featured disturbed sleep [2].

Though the core clinical features of delirium were already spelled out in the sixteenth century, diagnostic criteria have continued to evolve. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), due out in May 2013, will likely define delirium as a disturbance in the level of awareness or attention (rather than consciousness as in the previous edition), marked by the acute or subacute onset of cognitive changes attributable to a general medical condition. It tends to have a fluctuating course and must not be solely attributable to another cognitive disorder, although delirium is common in the setting of major neurocognitive disorders [3]. DSM-V may also subcategorize delirium into hyperactive, hypoactive, and mixed varieties [4]. Patients with hyperactive subtype of delirium are typically agitated and restless. Hypoactive patients have decreased level of consciousness and psychomotor retardation. Patients with mixed subtype have features of both.

EPIDEMIOLOGY AND OUTCOME OF DELIRIUM

Delirium is a common and serious problem among older persons at every healthcare interface. It occurs in 10-60% of the older hospitalized population and is unrecognized in 32-66% of cases [5]. In a cohort study conducted at three university-affiliated teaching hospitals, delirium was found to be present at admission in 12% of patients (88 of 727 medical and surgical admissions to non-intensive-care wards) [6]. At hospital discharge, and at 3-month follow-up, there was a significant increase in deaths, nursing home placement, and functional decline in patients with delirium compared to those without delirium. Other studies have reported mortality rates of 10-26% among patients admitted with delirium and 22-76% in those who develop delirium during hospitalization [7-8]. A higher post-discharge mortality rate was also noted [8]. According to two studies, the prevalence of delirium among patients aged 65 and above in the emergency department (ED) was about 10% [9-10]. Mortality rate was higher for the patients sent home from ED with delirium compared to those without delirium [10].

Delirium has been reported in up to 80% of patients in intensive care units (ICU), especially affecting high risk elderly and ventilated patients [11], but most studies are either from one or few centers. Two recent international studies found a prevalence of delirium in ICU of 32.3% and 64.4% [12-13]. Delirium was associated with increased ICU and hospital mortality, and longer ICU and hospital length of stay (LOS). Delirium is also very common in post-surgical patients. In a review of 26 studies, the incidence of postoperative delirium was found to be 36.8% (range, 0% to 73.5%). Rates were highest for patients after coronary artery bypass graft (17% to 74%), and ranged from 28% to 53% after orthopedic surgery, and 4.5% to 6.8% after urological surgery [14].

PATHOPHYSIOLOGY

A firm understanding of the pathophysiologic mechanisms of delirium remains elusive despite the high prevalence and seriousness of this condition. Recent modalities used to understand the pathophysiology include neuroimaging, electroencephalography (EEG), and neurotransmitter studies.
Functional neuroimaging during and after delirious states using xenon-enhanced computed tomography (XeCT) or single-photon emission CT (SPECT) scan in geriatric patients has demonstrated a reduction in overall cerebral blood flow (CBF). Prolonged reduction in CBF triggers apoptosis/autophagy causing long-term cognitive impairment [15]. These findings are consistent with the clinical observation of increased propensity for dementia in patients with recurrent or prolonged delirium. Electroencephalography (EEG) abnormalities characteristically associated with delirium include occipital slowing, peak power and alpha decrease, delta and theta power increase, and slow wave ratio increase during active delirious states. These findings have been shown to correlate well with cognitive performance and delirium severity [16].

Though the exact role of neurotransmitters in the pathogenesis of delirium is not completely elucidated, acetylcholine seems to play a major role. A review of twenty-seven studies by Campbell and colleagues found an association between the anticholinergic activity of medications and either delirium, cognitive impairment, or dementia in all but two studies [17]. Dopamine is the other major neurotransmitter implicated in delirium, and serotonin, gamma-aminobutyric acid (GABA), and glutamate may also play important roles [18]. Beta-endorphins, melatonin [19], and cytokines such as interleukin-1 and interleukin-6 [20] which disrupt blood-brain barrier [21] may contribute towards the pathogenesis of delirium.

PRESENTATION AND DIAGNOSIS

A thorough history and physical examination is key to the prompt and accurate diagnosis of delirium. Most delirious patients may not be able to provide a complete or reliable history and in such situation family members or other caretakers, including nursing staff, can provide valuable information. The first clue usually is an acute change in behavior (agitated, unusually quiet), mental status (confused, disoriented, hallucinations, delusions), or physical function. Reversal of the sleep wake cycle may also be present. A prodromal phase characterized by sleep disturbance, frequent calls for assistance, and increased anxiety may be identifiable before the onset of clinical delirium [22]. The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR) [23] is presently the gold standard for the diagnosis of delirium. It includes the following criteria:

• Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

• A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.

• The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition, substance intoxication or withdrawal, use of a medication, or toxin exposure, or a combination of these factors.

The Neurocognitive Disorder Work Group which developed the diagnostic criteria for the soon to be released DSM-V proposed a few changes [24]. “Disturbance of consciousness” is replaced by “Disturbance in level of awareness” since consciousness is too nebulous a term to describe the symptoms of delirium. They also call attention to visuospatial impairment and impairment in executive function as key symptoms of delirium, and clarify that preexisting neurocognitive disorders do not account for the cognitive changes.

Despite the existence of a large number of scales to screen, diagnose, and assess the severity of delirium, there is no unanimity about which scale best serves each purpose (Table I) [25-29].

The scales considered most reliable and used most widely are: the Confusion Assessment Method (CAM) – an excellent diagnostic tool; the Delirium Rating Scale and its revision (DRS and DRS–R-98) and the Memorial Delirium Assessment Scale (MDAS) – for measuring severity; and the NEECHAM confusion scale (Neelon and Champagne) – a quality screening [25]. In the intensive care unit, the CAM – ICU has shown to be a better predictor of outcome than the Intensive Care Delirium Screening Checklist (ICDSC) [26-27]. Due to the fluctuating course periodic assessment is essential.

Delirium must be distinguished from dementia and depression. This might be especially challenging when there is no previous known diagnosis of dementia since dementia cannot be diagnosed with certainty in the presence of delirium. Furthermore, hypoactive delirium may

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**TABLE I**

**ASSESSMENT TOOLS USED IN DELIRIUM**

<table>
<thead>
<tr>
<th>SCREENING</th>
<th>ASSESSING SEVERITY</th>
</tr>
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<tbody>
<tr>
<td>Confusion Assessment Method (CAM)</td>
<td>Delirium Detection Scale (DDS)</td>
</tr>
<tr>
<td>Intensive Care Unit – CAM (CAM–ICU)</td>
<td>Delirium Assessment Scale (DAS)</td>
</tr>
<tr>
<td>Intensive Care Delirium Screening Checklist (ICDSC)</td>
<td>Delirium Index (DI)</td>
</tr>
<tr>
<td>Bedside Confusion Scale (BCS)</td>
<td>Delirium Rating Scale revised 98 (DRS-R-98)</td>
</tr>
<tr>
<td>Clinical Assessment of Confusion-A &amp; B</td>
<td>Memorial Delirium Assessment Scale (MDAS)</td>
</tr>
<tr>
<td>Clock Drawing Test (CDT)</td>
<td>Neelon and Champagne Confusion Scale (NEECHAM)</td>
</tr>
<tr>
<td>Cognitive Test for Delirium (CTD)</td>
<td>Delirium-O-Meter (DOM)</td>
</tr>
<tr>
<td>Confusion Rating Scale (CRS)</td>
<td></td>
</tr>
<tr>
<td>Neelon and Champagne Confusion Scale (NEECHAM)</td>
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mimic depression (Table II) [30]. The Delirium Rating Scale – Revision-98 (DRS–R-98) successfully differentiates delirium from dementia and depression [25]. Since dementia is the most common risk factor for delirium, tools such as Mini-Mental Status Exam (MMSE) or Saint Louis University Mental Status examination (SLUMS) can be used to identify high risk patients in hospitals and long-term care facilities before the onset of delirium [31-32]. Similarly, depression screening tools such as Geriatric Depression Scale (GDS) may help distinguish depression from hypoactive delirium [33]. All three of these tools have been translated into Arabic.

CAUSES OF DELIRIUM

Most of the causes of delirium can be encompassed within the mnemonic “DELIRIUMS”:

- **DRUGS** - some commonly used drugs have very high propensity to cause delirium, whereas others are of moderate to low risk (Table III).
- **EMOTIONAL STATE** - such as depression that affects attention and thought process.
- **LOW OXYGEN STATES** - such as pulmonary, cardiac, or cerebrovascular event.
- **INFECTIONS** - urinary tract infection, pneumonia, cholecystitis, or meningitis [34].
- **RETENTION** - of urine or feces, especially the former can cause delirium even without infection [35-36].
- **ICTAL STATES** - a rare cause, but if the history suggests partial seizures or absence seizures, an EEG can be helpful.
- **UNCONTROLLED PAIN** - an often overlooked cause of delirium. A judicious trial of pain medication round-the-clock may be justified in cases where it is unclear if the patient is in pain [37].
- **METABOLIC ABNORMALITIES** like hypo- or hypernatremia, hypo- or hypercalcemia, hypoglycemia, metabolic acidosis, and many others.
- **SUBDURAL HEMATOMA**.

Iatrogenic conditions such as surgery, anesthesia, bladder catheterization, physical restraints, overmedication, immobilization, and the hospital environment itself may lead to some of the above triggers and cause delirium or exacerbate pre-existing delirium. In fact, these are the conditions under which delirium most often develops. Though the above-mentioned causes can precipitate delirium in any patient, the elderly, frail, and malnourished patient is especially vulnerable. Dementia is one of the most common risk factor for delirium, and, conversely, delirium portends an increased risk for future dementia.

Medications are an important cause of delirium in the elderly and require particular attention. High-risk medications can trigger delirium even when used at proper recommended dosing. This is particularly true with centrally-acting drugs. Mechanisms likely include imbalances in neurotransmitters (e.g. acetylcholine, dopamine, serotonin, etc.), age-related alterations in pharmacokinetics and pharmacodynamics, polypharmacy, and drug-drug interactions. Though almost any drug can cause delirium in susceptible

| TABLE II | DIFFERENTIATING DELIRIUM FROM DEMENTIA AND DEPRESSION |
|-----------------|-----------------|-----------------|
| **DELIRIUM** | **DEMENTIA** | **DEPRESSION** |
| Consciousness  | Altered and fluctuating, clouded | Not clouded until terminal stage | Typically clear |
| Orientation    | Disoriented and disorganized | Disoriented in later stage | Oriented or unable to assess due to apathy |
| Onset          | Acute or subacute | Chronic | Acute, subacute or chronic |
| Course         | Fluctuating and reversible | Steadily progressive and irreversible | Steady and reversible |
| Attention      | Short span | Normal | Normal |
| Psychomotor Changes | Common (hypoactive or hyperactive) | Late feature unless depression or apathy present | Normal or hypoactive |
| Hallucinations | May be present | Usually absent | Absent |
| Sleep Wake Cycle | Disrupted | Preserved until late | Usually preserved |
| Speech         | Incoherent | Difficulty finding words and names, aphasis in late stage | Slow |

| TABLE III | MEDICATION OR CATEGORIES OF MEDICATION ASSOCIATED WITH DELIRIUM [41] |
|--------------------------|--------------------------|--------------------------|
| **High Risk** | | |
| Benzodiazepines | Muscle relaxants |
| Diphenhydramine | Neuroleptics |
| Dopamine Agonist | Scopolamine |
| Mepedrine | |
| **Moderate to Low Risk** | | |
| Acetylcholine esterase inhibitor | H₂-blocker |
| Anticonvulsant | Meclizine |
| Antidepressants | Memantine |
| Antispasmodic | Metoclopramide |
| β-blocker | Narcotic other than Meperidine |
| Clonidine | NSAIDs |
| Corticosteroids | Sedative hypnotics |
| Digoxin | Some antibiotics and antivirals |

NSAIDs: non-steroidal anti-inflammatory drugs
individuals, initiation of drugs like benzodiazepines, muscle relaxants, and medications with anticholinergic properties have higher propensity to cause delirium. Narcotic analgesics can generally be used safely in older persons, but meperidine is of particularly concern due to its anticholinergic activity and bioaccumulation of its active metabolite normeperidine. The antihypertensive agents reserpine and clonidine are more commonly implicated in delirium than other drugs like thiazide diuretics, calcium channel antagonists, ACE inhibitors, and β-blockers. Tricyclic antidepressants with their high anticholinergic activity carry moderate risk of causing delirium, while selective serotonin reuptake inhibitors (SSRIs) have less propensity unless they cause hyponatremia [38]. Finally, one must be cognizant of cumulative side effects, such as the similar anticholinergic activity of multiple drugs prescribed for unrelated conditions.

DELIRIUM WORKUP

Though a detailed history and physical examination is the key to establishing a diagnosis, laboratory findings and imaging modalities are often necessary to identify the underlying cause or causes of delirium. A complete blood cell count (CBC) with differential can help confirm an infection or detect anemia. A metabolic panel will detect electrolyte abnormalities or reveal renal or hepatic abnormalities. Other tests that may prove useful include a urinalysis, thyroid function, vitamin B12, folic acid, thiamine, glucose, alcohol and drug levels, toxicology screen, and cultures of blood or body fluid.

A radiograph of the chest may diagnose pulmonary or cardiac pathology. Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head will identify stroke, hemorrhage, or structural abnormalities. Electrocardiogram (EKG) and cardiac enzyme serology are indicated for delirious patients in whom the risks of cardiac ischemia are present [39]. Electroencephalogram (EEG), though not routinely indicated, usually shows diffuse slowing of waves in delirium but may show fast activities in delirium tremens associated with alcohol withdrawal. In rare case, if clinically indicated, lumbar puncture must be performed to rule out CNS infection.

To date, there are no serum biomarkers diagnostic of delirium, but higher levels of calcium-binding protein S100B are found in patients with delirium and might play a future role in the diagnostic workup [40]. At present, however, there is insufficient evidence to support using S100B as a biomarker for delirium.

MANAGEMENT AND TREATMENT OF DELIRIUM

Management of delirium is through a multifactorial approach which includes preventive strategies, supportive therapies, and treatment of underlying medical causes. Educating families, patients, and caregivers — including hospital staff — regarding the causes, course, and prognosis is an integral part of the management of delirious patients. Preventive methods include avoiding restraints, limiting number of medications, ambulating patients, improving vision and hearing by providing appropriate glasses and hearing aids, keeping rooms brightly lit during the day but quiet and dark during the night, avoiding appropriate glasses and hearing aids, keeping rooms brightly lit during the day but quiet and dark during the night, avoiding bladder catheterization unless necessary, frequent assessment of patients, and aggressive but judicious use of medications to treat pain [41-42]. Though most studies that used the multifactorial approach showed an improvement in duration of delirium and in post-delirium function, only one showed reduction in mortality [43]. The TADA approach (Tolerate, Anticipate, and Don’t Agitate) is used for patients with delirium or at risk for delirium, especially older patients with dementia, while the underlying causes are being investigated or treated [44]. Videos depicting scenarios and use of TADA approach can be found online at http://www.stlouis.va.gov/GRECC/Education.asp. Multidisciplinary intervention by a proactive consultation team of doctors, nurses, and pharmacists can reduce the incidence of delirium by more than 25% [45].

The cornerstone of treatment of delirium is identifying the underlying cause, and every effort should be made to address potentially reversible causes early. Adequate nutrition and hydration should be provided, preferably orally. If this is not possible then the parenteral route can be used. Aspiration precaution should be instituted but strict precautions such as ‘NPO’ need to be balanced with risk of dehydration and/or malnutrition.

No medication is yet approved by the Food and Drug Administration (FDA) for treatment of delirium in the United States. A systematic review of prospective studies on the use of antipsychotic medications in delirium found only six single-agent studies and seven comparison studies, of which only one was a placebo-controlled trial. The placebo-controlled trial found no statistically significant difference in mean delirium severity scores between the two groups. The other studies reported improvements in delirium severity or resolution, but it was not clear from these studies to what these changes were attributed to [44]. Despite lack of evidence, neuroleptics such as haloperidol remains a mainstay for the treatment of psychotic symptoms of delirium, whereas the use of short-acting benzodiazepines (such as lorazepam) is only justifiable in delirium secondary to withdrawal of alcohol and may potentiate delirium in other cases. Though case reports have described the use of cholinesterase inhibitors in the management of delirium, a systematic review of Cochrane database did not support their use [46]. A randomized double-blinded placebo-controlled multicenter trial showed that rivastigmine (Exelon) did not decrease duration of delirium and increased the mortality of patients with delirium in the intensive care unit [47]. The study was stopped prematurely due to a statistically significant increase in mortality in the intervention group. At this time, the recommendation is for use of medications in delirium only as a final resort, when non-pharmacological interventions have failed, and is based on consensus and not on evidence based studies.
Delirium is an acute and common problem often affecting frail and older persons in the acute care hospital, but can develop in any setting. It is associated with serious complications but can also be treatable if diagnosed early and managed properly. Preventive measures should be implemented in high risk patients, such as those with malnutrition, polypharmacy, infections, previous delirium, or dementia. Despite precautions, delirium is unavoidable in some cases and clinicians should be familiar with the typical features and varied presentations of this condition. Diagnosing delirium can be based on the DSM criteria, though multiple useful screening tools exist. Since delirium is almost always triggered by an underlying condition, an aggressive search for the causative insult(s) is essential in order that a targeted intervention be started promptly. Although there is neither any medication approved by the FDA for the treatment of delirium nor any robust evidence supporting the benefit of medications, there is general consensus that drug intervention can be attempted when non-pharmacological interventions have failed.

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Occurring in approximately 20% of hospitalized elderly patients, delirium is the most common psychiatric syndrome in acutely ill general medical and surgical patients. Fifteen to 30% of delirious patients expire, and others are prone to a variety of complications: falls, pressure ulcers, oversedation, dehydration, and others. Almost any acute illness can cause delirium in the elderly, but the most common offenders are acute infections and drugs. Many patients have a pre-existing dementia. The first step in arriving at a correct diagnosis is to distinguish delirium from other psychiatric syndromes. Delirium occurs in the elderly due to the interaction between various predisposing and precipitating factors[2,3]. The commonest predisposing factors for delirium are older age and an underlying cognitive impairment. Impairment in vision, severe comorbid illness and renal dysfunction are additional predisposing factors[8]. Precipitating factors include the use of physical restraints, malnutrition, more than three medications added to the treatment regimen, the use of bladder catheters and any iatrogenic event[9]. It is estimated that almost a third of the cases of delirium in the elderly go un Also rule out fecal impaction urinary retention (bladder U/S, in-and-out catheter) Infected decubitis ulcer Treatment and Management Identify and correct the correctibles Multiple causes in elderly Careful monitoring Place patient near nursing station (1:1) VS, I & O, O2 Reduce psychiatric symptomatology Agitation Psychosis Discontinue nonessential medication Drug toxicity and drug induced delirium is most common See Medical Letter. Risks of Using v Not Using Atypical Antipsychotics Increased mortality in elderly patients with dementia-related psychosis 17 placebo controlled trials Modal duration of 10 weeks Risk of death in treated patients 1.7 times that seen in placebo treated patients Varied