1. Introduction

1.1 Ventilator associated pneumonia

Ventilator associated pneumonia (VAP) is one of the sub-types of nosocomial acquired pneumonia occur in patients admitted to ICU who are under ventilator assistant mechanical ventilation occurring more than 48 h after patients have been intubated and received mechanical ventilation. Between 250,000 and 300,000 cases per year occur in the United States solely, which is an incidence rate of 5 to 10 cases per 1,000 hospital admissions\(^1\). The incidence of VAP increases with the duration of mechanical ventilation higher in day 10 compare to day five\(^2\), and it is associated with high mortality rates (0-50\%) in ICU patients, and pneumonia accounts for second cause of death in ICU patients\(^3\), although Using various scoring systems for the mortality prediction along with the guideline-based medicine have helped decrease in VAP mortality rates\(^4,5\). Although mortality of viral VAP is not determined in ICU patients, the scoring systems provide an acceptable clinical index for such cases [46]. The misuse of insufficient dose or inappropriate antibiotic will lead to outgrow multi drug resistant serotypes of bacterial VAP and induce higher mortality\(^6\). This high mortality rate also depends on the type of underlying disease, with highest mortality attributable to VAP in patients with trauma or acute respiratory distress syndrome\(^7\), and the type of organism affecting the patient. Higher mortality rates have been explored in VAP caused by *Pseudomonas aeruginosa* (in patients with underlying respiratory problems) \(^8\), *Acinetobacter*, and *Stenotrophomonas maltophilia* than those associated with other organisms\(^9\).

*Bacterial VAP can be* due to colonization and spread of organisms from oropharynx, sinus cavities, nares, dental plaque, gastrointestinal tract, patient-to-patient contact, and the ventilator circuit to the lungs\(^10\). Essentially, each ICU should have an established protocol in place to initial empirical therapy based on previously accepted guidelines modified by local knowledge of prevalence of resistant serotypes unique to that ICU. Notably, empiric therapy should be both appropriate by using more specific antibiotics and adequate by using correct dose and good penetration to the site of infection\(^11\). Duration of antibiotics are also been a point of controversy; although 8 days of therapy has been effective in non-resistant organism, but duration of antibiotic therapy for multiple drug resistant (MDR) organism such as *P aeruginosa* and *Acinetobacter* spp, is unknown\(^12\).
On the other hand, a key point in management of MDR VAP is rapid diagnosis of VAP and providing culture and anti-biogram in detecting the responsible organism. The antibiotic duration for patients with MDR VAP remains a controversial issue. Several serum biomarkers have been applied as potential biomarker contributing to guide antibiotic use in patients with VAP caused by MDR pathogens. Previously, pro-calcitonin (PCT) has been broadly used as a marker for community acquired pneumonia (CAP) and VAP\textsuperscript{13,14}, however it does not incorporate into hospital acquired pneumonia (HAP). Using PCT has shortened duration of anti-microbial treatment in VAP\textsuperscript{15} in which patients with MDR VAP whose serum PCT concentrations are less than 0.5 ng/mL or decreased by 80% or more, compared with the first peak concentration, antibiotics may be terminated 3 days after initiation\textsuperscript{16}. On the other hand usefulness of other bio-markers such as C reactive proteins (CRP) have yielded to conflicting data's\textsuperscript{17}, probably due to acute phase reactant release in ICU patients such as IL-6 and TNF-\alpha which stimulate CRP release to surmountable amounts.

Our current data on epidemiology, pathogenesis, clinical importance, and risk factors of viral VAP and viral pneumonia in ICU has many pitfalls due to some challenges\textsuperscript{18}. First, the diagnosis of viral VAP in critically ill patients requires a high clinical suspicion combined with bedside examination, radiographic examination, and microbiologic analysis of respiratory secretions. Besides, the presence of indolent viral VAP in a critically ill patient makes diagnosis more challenging and increases the mortality rate of patients. It is important to investigate these viral markers in VAP to probe them earlier and estimate their role in increasing mortality rate. ICU patients assumed as immunocompetent are also at risk for Herpes simplex virus (HSV) and cytomegalovirus (CMV) VAP\textsuperscript{19}. Although CMV reactivation assumed to increase morbidities like increased length of stay in the ICU but impact on mortality particularly in patients with low CMV-DNA plasma levels is in doubt\textsuperscript{20}. Currently there is increasing tendency to CMV infection among ICU patients. One simple explanation is that any bacterial colonization in ICU patients promotes the release of immunomodulatory cytokines and lead to reactivation of CMV\textsuperscript{21}, and reactivation from the latency induces CMV infection. Because of nonspecific signs and symptoms ICU patients are rarely monitored routinely for active CMV infection, the development of active CMV infection could remain under-diagnosed in critically ill patients.

The 2009 H1N1 influenza virus pandemic has highlighted another challenge faced by intensivists in managing severe influenza A, especially for those at high risk of severe respiratory disease in ICUs\textsuperscript{44}. Thus, intensivists should consider performing rapid diagnostic tests and specific scoring for drug resistance genotyping for high risk patients especially in tertiary care centers\textsuperscript{45}.

2. Hyperglycemia and hypoglycemia in ICU

Essentially, ICU admitted patients encounter a profound hyperglycemia due to stress hormone surge, corticosteroid usage, and inhibition of insulin release of sepsis or trauma induced mediators\textsuperscript{22}. Hyperglycemia could harm ICU patients by increase susceptibility to sepsis and increase mortality of critically ill patients\textsuperscript{23}. It is supposed to have a tight control of hyperglycemia in ICU patients although threshold of blood glucose is still
controversial. As a matter of fact, glucose monitoring and route of insulin injection is mainstay of hyperglycemia control in ICU patients. Nonetheless, different studies have suggested various blood glucose levels but majorly 180 mg/dl has considered the safe treatment threshold and 140-180 for target glucose level\textsuperscript{24,25,26,27,28}. It is widely assumed that sampling in ICU patients could also be a bottleneck in glucose tight control as catheter sampling is easy but have danger of contamination with IV fluids, whether fingerprints sampling may be inaccurate in patients with edema or anemia\textsuperscript{29}. On the other hand, insulin therapy induced hyperglycemia may cause severe neurologic damages while neurologic symptoms of hypoglycemia are difficult to detect in critically ill patients, but they are a real concern\textsuperscript{30}. Severe hypoglycemia <40 mg/dl could occurred in almost high proportion of patients in intensive insulin therapy and could majorly increase mortality rates of patients\textsuperscript{31,32}. Besides, all the studies with target glucose concentration of 80 to 110 mg/dl showed increased rates of hypoglycemia\textsuperscript{33}. Notably, even a blood glucose target of 180 mg/dl or less resulted in lower mortality than did a target of 81 to 108 mg/dl\textsuperscript{34}.

3. Venous thromboembolism (VTE) and Pulmonary Embolism (PE)

Venous thromboembolism (VTE) is a common and lethal complication in critically ill patients, due to several predisposing factors such as pre morbid conditions (e.g., trauma, major surgeries, malignancy, sepsis), invasive interventions like central venous catheterization, and prolonged immobility\textsuperscript{35}. The incidence of VTE is reported variously in different studies based on the population, prophylactic interventions and screening methods. Patients in intensive care unit have a higher risk of lower limb deep venous thrombosis (DVT) in comparison with other hospitalized patients which may be undiagnosed in considerable number of cases\textsuperscript{36}. On the other hand, VTE could remain unrecognized in the intensive care unit because of the difficulty in eliciting signs and symptoms from intubated, sedated patients. It is likely that quite large number of patients under mechanical ventilation with unexpected episodes of tachycardia, hypotension, or hypoxia may have unnoticed pulmonary embolism (PE)\textsuperscript{37} which could be diagnosed based on Geneva score with an acceptable predictive accuracy in low and intermediate-probability groups\textsuperscript{38}. Undiagnosed or barely suspected PE may also lead to delay weaning patients from mechanical ventilation. Intensive care unit patients, who have reduced cardiopulmonary reserve, are prone to have significant complications of PE. Recent data suggest that the duration of therapy and recurrence rate is associated with persistently elevated levels of d-dimer\textsuperscript{39}. Long-term treatment of thrombosis with the low-molecular-weight heparin has been shown to be associated with fewer thromboembolic recurrences in ICU patients\textsuperscript{40}.

4. Management of ICU-associated agitation by dexmedetomidine

Agitated delirium is common complication occurs commonly in patients undergoing mechanical ventilation in ICU, and is often treated with haloperidol despite concerns about its adverse effects such as unpredictable hepatic toxicity and cardiotoxicity\textsuperscript{41}. Inadequate sedation in ICU particularly in intubated patients adversely affects their
morbidity and mortality. Use of sedatives during agitation while patient under mechanical intubation precludes further extubation. Other than that agitation in intensive care may be associated with self-extubation, removal of vascular catheters, increased oxygen consumption and failure to cooperate with treatment. Drug of choice should be effective, safe, titrable, rapidly acting agent that has both sedative and analgesic activity, and could prevent anxiety and unpleasant memories. The newly introduced drug, Dexmedetomidine, a novel selective α2-agonist with sedative and anxiolytic properties, have showed particular utility in ICU-associated delirious agitated patients under mechanical ventilation without inducing excessive sedation, with fewer side effects than haloperidol, little interaction with other drugs and easily titrable. Studies have reported the successful use of dexmedetomidine in this context although multi-centric clinical trials may needed to establish those assumptions. Dexmedetomidine is more effective than conventional haloperidol therapy for the treatment of combined agitation and delirium in intubated patients in the ICU; besides Dexmedetomidine reduce the need of extra sedative known to cause agitation. Its administration superiority to traditional sedatives is reliably shown that has reduced ICU length of stay, hastened liberation from mechanical restraint, reduced the need for supplementary sedation, reduced QTc interval prolongation and possibly reduced the need for tracheostomy. In a study in comparing dexmedetomidine and propofol in patients requiring sedation in ICU, dexmedetomidine revealed safer and protect against myocardial infarction. In addition, some studies have proposed that patients who receive a dexmedetomidine bolus have no clinically significant hypotension or increased epinephrine requirement but others not. Dexmedetomidine induce no respiratory depression and should be considered for patient failing spontaneous breathing due to agitation or anxiety. On the other hand, in dose related hypotension and bradycardia bolus dexmedetomidine is not recommended. Besides, clinicians should consider higher starting dose of dexmedetomidine if used as monotherapy.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Consideration</th>
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<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>0.2-1.5 mcg/kg/hr patients failing spontaneous breathing trials secondary to agitation</td>
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<tr>
<td>Haloperidol</td>
<td>2.5-5mg IV q 15 min prn/ 2.5-5 mg PO q6 hr</td>
<td>Caution if baseline QTc &gt;440 msec</td>
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<tr>
<td>Aripiprazole</td>
<td>10-15 mg po daily</td>
<td>Consider when baseline QTc&gt;440 msec</td>
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<tr>
<td>Quetiapine</td>
<td>50-200 mg po q12 hr</td>
<td>Consider if sedative properties desired</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.5-1 mg po q12 hr</td>
<td>Caution baseline QTc &gt;440 msec</td>
</tr>
<tr>
<td>Propofol</td>
<td>1 mg/kg loding+1-3mg/kg/h</td>
<td>Consider vasodilation risk</td>
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Table 1. Pharmacologic Treatment for Delirium.
5. References


Thoracic Surgery congregates topics and articles from many renowned authors around the world covering several different topics. Unlike the usual textbooks, Thoracic Surgery is a conglomerate of different topics from Pre-operative Assessment, to Pulmonary Resection for Lung Cancer, chest wall procedures, lung cancer topics featuring aspects of VATS major pulmonary resections along with traditional topics such as Pancoast tumors and recurrence patterns of stage I lung disease, hyperhidrosis, bronchiectasis, lung transplantation and much more. This Open Access format is a novel method of sharing thoracic surgical information provided by authors worldwide and it is made accessible to everyone in an expedite way and with an excellent publishing quality.

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