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Review Article

Nontuberculous Mycobacteria in Critical Care

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Abstract

In critically ill patients infections is a common problem and their management is difficult because of some reasons such as delayed diagnosis, difficulties in recognizing causative microorganisms, and antibiotic-resistant strains. In this review article we briefly discussed Non Tuberculosis Mycobacterium (NTM) infections which have worldwide increasing in incidence and can lead to respiratory failure. Patients with NTM infection who experience lung disease are at high risk of respiratory failure and acute respiratory distress syndrome. Brief discussion about infections in burn and immune compromised patients is included.

Keywords: Non tuberculosis mycobacterium; Lung disease; NTM infection; Mycobacterium avium complex

Introduction

Recent studies inpatients, who are hospitalized in Intensive Care Unit (ICU), show that 51% of them have infections, and 71% are given treatment. Bacterial and some fungal infections, as opportunistic microorganism are the primary concern. Hospitalizing in ICU is associated with increasing in mortality rate and excess expenses. Pharmacokinetics, absorption, distribution, metabolism, and excretion of drugs experience many changes in critical illness [1].

NTM, are a group of mycobacteria which is not a causative organism of tuberculosis or leprosy, so they called as Mycobacteria Other Than Tuberculosis (MOTT). NTM bacteria are a family of small, rod-shaped bacilli which have more than 150 species. Atypical mycobacteria have different favor in choosing their environment and are identified as environmental mycobacteria [2,3]. NTM are the causative organisms in pulmonary diseases like tuberculosis, lymphadenitis, skin disease, or disseminated disease. Major clinical manifestations of NTM Infections are presented in Table 1 [4]. In 1950s, they were accepted as human pathogens [5]. Unlike tuberculosis and leprosy, spreading NTM infections from one person to another person is rare. Environmental exposure is the major way of contagion [6,7]. The risk of getting infected by a particular species of NTM is dependent on pathogenicity of microorganism, the method of exposure and frequency of exposure [8]. In the last decade, (NTM) infections have worldwide increasing in incidence and mortality [9,10]. The reasons for this increase are not obvious. But increasing incidence of acquired immune compromised syndrome, cancer, diabetes mellitus, chronic lung injuries, and continues supportive ventilation could be causative [11,12].

Non Tuberculosis Mycobacterium Infection

A retrospective study in medical center of Taiwan from January 1999 to June 2007 was planned to evaluate medical ICU patients whose respiratory specimens were positive for NTM. They defined tree group of patients, one group with NTM pulmonary infection, the other with NTM colonization and a control group who have culture negative samples for mycobacteria. Clinical sign, symptoms and outcomes were compared. Their finally result was that, increment in mortality rate in patients who have NTM pulmonary. Suitable treatment against NTM would followed by better result [13].

Pulmonary Tuberculosis (TB) needs invasive workups or treatment, but NTM infection with minimal clinical manifestation and stable radiographic feature requires closely observation except patients who are immune compromised so appropriate method for diagnosing is necessary. Molecular gene analysis including sequencing of16S rRNA and *hsp65* is recommended to be more accurate than conventional biochemical methods [14]. When the clinicians, according to patient condition, decide to initiate treatment against NTM infection, there are some considerable points such as side effects of drugs and high relapse rate [8]. So 12 months of culture negativity would be one of the noticeable goals in their management. It is also important that sputum sampling is required every 1-2 months. Macrolides (clarithromycin or azithromycin) have major role in management of Mycobacterium avium-intracellular lung disease. The standard elective regimen prolongs 18-24 months. The combination of rifamycin (rifampicinor mycobutin), myambutol and a macrolide is suggested in this regimen. Amino glycosides (amikacin or streptomycin) could be adjoining on regimen in severe cases. They usually added for the first 2 or 3 months of treatment period. The optional regimen recommended to cure mycobacterium kansasii infection is similar to anti TB drugs except for pyrazinamide [15].

Mortality among burn patients is mainly because of infections especially after recovery from the initial burn injury. Gram-positive cocci like Staphylococcus aureus, gram negative bacilli such as Pseudomonas aeruginosa, less commonly fungi and viruses are known as causative organisms. Risk factors such as loosing skin integrity, immune compromised condition, inhalation damage, and continuity in having vascular catheters would higher the risk of developing NTM infections. On the whole, NTM infections in burn patients appear to be rare so routine screening or exam for mycobacteria is not required. However, it is noticeable that in patients who are failing to clinically improvement despite suitable recognition and management of typical bacterial and fungal pathogens accompanied with burns infections with NTM should be in the differential diagnosis [16].

In a study, HIV-infected patients who have disseminated NTM

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Table 1: Major clinical manifestations of NTM Infections [4].

Syndrome	Frequent Causes	Uncommon Causes
Lung disease	*MAC*, *Mycobacterium kansasii*, *Mycobacteriumabscessus*	*Mycobacterium fortuitum*, *Mycobacterium malmoense*, *Mycobacterium szulgai*, *Mycobacterium scrofulaceum*, *Mycobacterium smegmatis*, *Mycobacterium simiae*, *Mycobacterium xenopi* Rare: *Mycobacterium celatum*, *Mycobacterium asiaticum*, *Mycobacterium shimodei*
Cervical and lymphadenitis	*MAC*	*Mycobacterium scrofulaceum*, *Mycobacterium malmoense*, *Mycobacterium abscessus*, *Mycobacterium fortuitum*
soft tissue manifestation	*Mycobacterium fortuitum*, *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium marinum*	*Mycobacterium haemophilum*, *Mycobacterium kansasi*, *Mycobacterium smegmatis*, *Mycobacterium ulcerans*
Skeletal (bones, joints, tendons) disease	*Mycobacterium marinum*, *MAC,Mycobacterium kansasii*, *Mycobacterium fortuitum* group, *Mycobacterium abscessus*, *Mycobacterium chelonae*	*Mycobacterium haemophilum*, *Mycobacterium scrofulaceum*, *Mycobacterium smegmatis*, *Mycobacterium terrae-nonchromogenicum* complex
Catheter-related infections	*Mycobacteriumfortuitum*, *Mycobacterium abscessus*, *Mycobacterium chelonae*	*Mycobacterium mucogenicum*
Disseminated infection	Patient with HIV infection: *Mycobacterium avium*, *Mycobacterium kansasii*	*Mycobacterium haemophilum*, *Mycobacterium genavense*, *Mycobacterium xenopi*, *Mycobacterium marinum*, *Mycobacterium simiae*, *Mycobacterium intracellulare*, *Mycobacterium scrofulaceum*, *Mycobacterium fortuitum*
	Patient without HIV infection: *Mycobacterium abscessus*, *Mycobacterium chelonae*	*Mycobacterium marinum*, *Mycobacterium kansasii*, *Mycobacterium haemophilum*, *Mycobacterium fortuitum*

Table 2: Guidelines for diagnosing NTM pulmonary disease [29].

Clinical and radiologic features indicative of mycobacterial disease
Positive Acid Fast Bacilli smear and/or moderate to heavy growth on medium in two clinical specimens (e.g., sputum or BAL)
Absence of other pathogens (e.g., tuberculosis, aspergillosis)
Underlying host conditions such as alcoholism, immunosuppressive conditions, chronic lung disease, cystic fibrosis, lung cancer
Failure of clearance of the NTM in sputum within 2 weeks after initiation of anti-mycobacterial therapy
When sputum evaluation in cavitary or non cavitary disease is negative: 1) Trans bronchial or open lung biopsy has histopathologic features of mycobacterial disease and NTM grows on culture 2) Trans bronchial or open lung biopsy does not grow the organism but has histopathologic features of mycobacterial disease and other probable causes for granulomatous disease have been ruled out.

infection between 2000 and 2013 were analyzed. Culture from several sterile specimens of blood and mesenteric lymph node caught. Mycobacterium Avium Complex (MAC) was the most frequent pathogen which is recognized in this study. They concluded that in patients who have acquired immune deficiency syndrome with low CD4 level have high mortality rate in disseminated NTM infection. Low level of CD4 is counted as a risk factor of this condition [17].

Increased Respiratory Failure has Association with NTM Infection

Exchange between blood gases including O_2 and CO_2 fulfill the need of metabolism. Any failure in this process result in hypoxemia, in the presence or absence of hypercarbia and finally Respiratory Failure (RF) happens. Acute Respiratory Failure (ARF) defines when these events occurred during several minutes to hours. In Chronic Respiratory Failure (CRF) happening events prolong many days [16,18]. Acute exacerbation of CRF can lead to a condition which is called ARF on CRF [19]. Measuring arterial blood gases including partial pressure of O_2(PaO_2) and partial pressure of CO_2($PaCO_2$) is the way to diagnosis RF.RF is defined in a patient respiring at sea level and at rest, when PaO_2 is lesser than 60 mmHg or $PaCO_2$ is more than 50 mmHg [18,20,21].

RF can cause patients to hospitalize in intensive care unit and make them dependent to mechanical ventilation. Tuberculosis, cardiogenic or non-cardiogenic pulmonary edema, pulmonary hemorrhage, pneumonia, diabetes, drug toxicity, neuromuscular disorders, chest wall deformities, Chronic Obstructive Pulmonary Disease (COPD), emphysema, refractory asthma, End-Stage Renal Disease (ESRD), malnutrition and acquired immune deficiency syndrome are several etiologies of RF [22-25]. In several studies the rule of RF etiologies as predisposing factors of NTM infection is mentioned [26-28]. A nationwide cohort study was designed to estimate the chance of developing RF in patients who have NTM infection, in comparison with the ordinary people. In this study they followed up a great group of patients with NTM infection for 4 years. They conclude that these patients have a greater risk to develop RF in comparison with the general population, especially in the first 6 months after diagnosis. Another finding was that, patients with other comorbidities particularly COPD and diabetes are in higher risk for developing RF. Mycobacterium avium complex infection is known as a great risk factor for respiratory failure. Finally they suggest that in order to prevent RF, an early diagnosis of NTM disease is necessary [29]. Recommended criteria suggested for diagnosing NTM lung disease are present in Table 2.

Acute Respiratory Distress Syndrome and NTM Infection

Acute Respiratory Distress Syndrome (ARDS) is a medical syndrome identified with generalized lung inflammation, severe dyspnea and hypoxia [30]. Diffuse lung injury is the main reason for ARDS. Toxic inhalation, pneumonia are some examples of direct injuries. For indirect damages sepsis could be a good example [31]. The diagnosis of ARDS is based on Berlin ARDS Definition which is presented in Table 3.

Table 3: The Berlin definition of ARDS [31].

Timing	Initiate of within 7 days of insult, or progression of respiratory symptoms
Chest imaging	Bilateral chest opacities on chest radiograph or computed tomography which cannot justified by other pathologies.
Origin of edema	The origin of edema is not because of cardiac failure or volume overload.
Oxygenation	Mild : 200 mmHg < PaO_2 /FIO_2 <300 mmHg with PEEP or CPAP >5 cmH_2O Moderate: 100 mmHg < PaO_2 /FIO_2 <200 mmHg with PEEP >5 cmH_2O Severe: PaO_2 /FIO_2 <100 mmHg with PEEP >5 cmH_2O

The Large Observation a cohort study designed in 50 countries from 5 continents to evaluate patients experience mechanical ventilation against non invasive ventilation. The samples gained from 459 medical ICUs. They concluded that this syndrome have association with a great mortality rate and appeared to be under identified, under managed and needing advancement in ARDS patients management [32].

ARDS caused by bilateral pneumonia or sepsis due to NTM infection is not common. Patients in these cases need intensive medical management and respiratory support, so recognizing these organisms as a cause of RF is significant [33-35].

Conclusion

NTM are opportunistic pathogens with increasing incidence in recent years. Patients with NTM infection who experience lung disease are at high risk of respiratory failure. In critically ill patients infections is a common problem and their management is difficult because of some reasons such as delayed diagnosis, difficulties in recognizing causative microorganisms, and antibiotic-resistant strains. Newer antimicrobial combinations and clinical trials are recommended.

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