Overview of Pneumonia in Indonesia

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INTRODUCTION

Pneumonia is a serious acute infection of the lung parenchymal that can major cause of morbidity and mortality in children and adults primary in low and middle income countries (LAMICs).[1] Sometimes it is a life-threatening respiratory infection among the older people throughout the world. Globally, pneumonia is a serious public health concern and a major cause of mortality.[2] An important reason for the increased global mortality is the impact of pneumonia on chronic diseases, along with the increasing age of the population and the virulence factors of the causative microorganism. Another problems of faced is the increasing number of multidrug-resistant bacteria, difficult-to-treat microorganisms, and the emergence of new pathogens that are a major problem for clinicians when deciding antimicrobial therapy.[2]

Known forms of pneumonia such as community acquired pneumonia (CAP), nosocomial pneumonia [hospital acquired pneumonia (HAP) and ventilator associated pneumonia (VAP)], and aspiration pneumonia. Nosocomial and CAP pneumonia are caused by various microorganisms such as viral, bacterial, parasite, and rarely fungi. The CAP showed an increased incidence associated with increasing patient age and the highest rates among adults aged between 65 and 79 years of age. In the USA the annual incidence of pneumonia was 24.8 cases per 10,000 adults, 63.0 cases per 10,000 adults aged between 65 and 79 years of age, and 164.3 cases per 10,000 adults aged.[3]

The increasing number of elderly people will be followed by an increase in the number of geriatric patients who have to obtain health services in relation to the vulnerability of this group to various acute conditions of health problems. Respiratory tract infections are the highest cause of death and the most significant cause of decline in quality of life in elderly people. Upper respiratory and influenza infections are common and continue to be pneumonia in the elderly.[4]

EPIDEMIOLOGY

Pneumonia is the most common cause of infectious disease related death among adults worldwide and is associated with age, HIV infection and smoking. In LAMICs, the dominant risk factors are HIV and smoke exposure. The incidence of community-acquired pneumonia requiring hospitalization was highest among the oldest adults, but in the majority of patients clinician unknown what pathogen as causes of pneumonia by current diagnostic tests. Respiratory viruses were detected more frequently than bacteria.[3] Countries with HIV endemic areas, pneumonia remains the most common cause of inpatient admission as many people are only diagnosed as HIV infected at presentation with pneumonia and progression to AIDS remains common. The association of pneumonia and HIV infection is dependent with CD4 level, decreasing CD4 followed by increases in incidence of pneumonia. Since successfully ART roll-out reduced the incidence of pneumonia among HIV infected adults but pneumonia outcomes among HIV infected people have been reported as similar to HIV uninfected patients given optimal therapy but patients with HIV often present with complex co-infections and co-morbidity.[1]

The study conducted by Azmi et al[5] of 62 hospitals in three Southeast Asian countries (Indonesia 42, Philippines 18, and Malaysia 2 hospitals respectively), the proportion of diagnoses of pneumonia (CAP and HAP) hospitalization in Indonesia was 1.5% (CAP 1.0% and HAP 0.5%), in Malaysia 6.4% (CAP 4.2% and HAP 2.2%) and in Philippines 19.9% (CAP 14.2% and HAP 5.6%). This result is consistent with the incidence rate of hospitalized pneumonia (CAP and HAP) in each country, highest incidence CAP 14,245 and HAP 5,615 cases per 100,000 patients discharges in Philippines, CAP 4,205 and HAP 2,187 cases per 100,000 patients discharges in Malaysia, and CAP 988 and HAP 538 cases per 100,000 patients discharges in Indonesia. Most inpatient pneumonia involves CAP, only 15.6% are HAP or VAP, but HAP and VAP account for > 25% of deaths.[6]

The 30-day mortality rate of CAP patients treated at the hospital has decreased. The first 30-day mortality rate 9.6% for the first period 1995 - 1999 decreased to 4.1% in the last period of 2010 - 2014, with a progressive down trend

-0.2% death / year. Several changes in the management of CAP and a general improvement in global care over time may have caused the observed outcomes.[7]

The prevalence of *S. pneumoniae* in CAP significantly varies between European regions, diagnostic *S pneumonia* was substantially higher in studies that performed more frequently a diagnostic polymerase chain reaction assay compared to all the other diagnostic tests included. Furthermore, S. pneumoniae was more likely to be confirmed as the cause of a CAP in studies with intensive care unit patients as compared to those with hospital- or community-treated patients. This study provides estimates of the average observed prevalence of *S. pneumoniae*, which could be used for projecting the health and economic benefits of pneumococcal immunization.[8]

PATHOGENS ETIOLOGY

Microbial identification of pathogens causing pneumonia is an important issue for optimum clinical management of pneumonia and is a major challenge globally, given the expanding rate of multidrug-resistant pathogens and the emergence of new pathogens.[2] Globally, *S pneumoniae* is a universally common cause of adult pneumonia[1,2], there are marked regional differences in the frequencies of other pathogens that are important to consider when selecting empirical antimicrobial treatment or determining the need for additional microbiological investigations.[1]

Pathogens other than *S pneumonia* are reported atypical bacterial pathogens, mycoplasma pneumonia is frequently reported and has caused macrolide-resistant problems. K pneumoniae has emerged as a frequent cause of severe pneumonia in both Asia and South Africa and substantial rates of multi-drug resistance have been observed. In South-East Asia Burkholderia pseudomallei, the causative agent of melioidosis is endemic and frequently presents as an acute severe pneumonic illness. The emergence of several novel respiratory viral infections from LAMICs in recent years serves to highlight the importance of continued vigilance to novel pathogens in patients presenting with acute pneumonia.[1] The recent publication reporting on the cause of the CAP microbial differs according to the severity of the clinical illness presentationn. A Spanish study regarding the relationship of microbial etiology of CAP and severity, concluded that pneumococcus is the most frequent pathogen in all sites of care. The second most frequent group of pathogens was intracellular microorganisms, followed by polymicrobial cases .[2]

An estimated prevalence of 19.3% to 34% was reported for *S. pneumoniae* in Europe. The diagnosis of pneumococcal pneumonia has increased significantly in recent years, mainly due to introduction of pneumococcal urine antigen test. Conversely, the incidence of pneumococcal pneumonia has probably decreased due to introduction of pneumococcal vaccine, as well as the decreased rate of smoking in most country.[2] High prevalence of HAIs in Vietnamese ICUs, mainly caused by Gram-negative bacteria with high rates of carbapenem resistance, and high levels of antimicrobial use illustrate the urgent need for capacity strengthening in both rational antimicrobial use and infection control efforts at national, regional and local levels.[9]

Catia Ciloniz et al found MDR pathogen in CAP at 6%, the two MDR pathogens were S aureus and P aeruginosa. Other researchers Aliberti et al[10] have reported that MDR microorganisms are involved in 3.3% to 7.6% of CAP cases in which the most commonly identified MDR pathogen was *methicillin-resistant S. aureus* (MRSA). However, despite the effort of collecting samples in pneumonia cases, approximately 50% of the cases remain without microbiological identification using conventional methods and recent studies have shown the importance of implementing new molecular platforms. Improve the microbiological diagnosis of pneumonia, thereby improving clinical management of cases, with shorter time to antibiotic therapy, better targeted antibiotic selection, more effective de-escalation and improved stewardship for pneumonia patients.[2]

P. aeruginosa is not a frequent pathogen in CAP. However, several studies have reported that in patients with severe CAP requiring ICU admission, *P. aeruginosa* was the causative agent in 1.8%–8.3% of the cases, with a case-fatality rate of between 50% and 100%. A recently published study found that 1% of cases were caused by MDR P. aeruginosa. Prior antibiotic treatment as the only risk factor associated with CAP caused by MDR *P. aeruginosa*.[2] Helmia Farida et al., conducted the first CAP etiology study in Indonesia to apply a complete set of microbiological tests. Their results found that influenza virus, *K. pneumoniae* and *S. pneumoniae* were the most common agents that had no correlation with the underlying disease, severity, and outcome of CAP. Viral infections were surprisingly common, either as single or combined etiology. PCR was instrumental in detecting most respiratory viruses. The use of PCR may, thus, enhance the appropriate use of antimicrobial agents.[11]

K. pneumoniae and other GNB were frequently observed. The high prevalence of K. pneumoniae and other GNB might, in part, be explained by the common carriage of these bacterial species in the nasopharynx of healthy individuals in the same area. The tropical climate with higher temperature and humidity in Semarang may increase the incidence of GNB infection, as those conditions promote the growth and virulence of GNB.[11]

S. pneumoniae infection was detected in only 13% of the patients, mostly by urinary antigen tests. Cultures frequently failed to grow this species, possibly due to the common use of antibiotics in the comunity.[11]

This prospective multinational study shows that Acinetobacter spp., Pseudomonas aeruginosa, Staphylococcus aureus, and Klebsiella pneumonia are the most frequent isolates from adults with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in 10 Asian countries, and these isolates are highly resistant to major antimicrobial agents. Multidrug-resistant rates were 82% and 42.8%, and extensively drug-resistant rates were 51.1% and 4.9%. Multidrug-resistant rate of K. pneumonia was 44.7%. Oxacillin resistance rate of S. aureus was 82.1%. All-cause mortality rate was 38.9%.[12]

BURDEN OF PNEUMONIA

CAP continues to be a cause of considerable morbidity and mortality in most parts of the world, being the most frequent infectious cause morbidity and mortality worldwide. Studies in the USA, Europe, Latin America, and the Asia-Pacific region attest to the fact that CAP has a substantial clinical and economic burden, a high rate of antibiotic resistance among the pathogens, and a significant effect on both immediate and long-term prognosis, as well as on the quality of life of infected patients. Given this high burden of disease, it is recommended that steps be taken to ensure appropriate treatment, ongoing surveillance for antimicrobial resistance among the common pathogens, and strategies, including vaccination, to prevent these infections.[13]

Since aging is a significant risk factor for this infection and given that in many areas of the world, such as Europe, the population is aging, an increase in incidence in the next decades is anticipated. The mechanism by which aging is associated with a risk for CAP is multifactorial, not simply related to chronological age, but frequently associated with (i) underlying comorbid conditions that more commonly occur in the aging population; (ii) a greater risk of being infected with antibiotic-resistant pathogens; (iii) social factors; and (iv) even place of residence.[13]

The results of this study show that there are differences in disease burden between CAP and HAP, similar to the results of previous studies performed in other countries. In all three countries, CAP was found to be a frequent cause of hospitalization in children under 5 years of age and those above the age of 50 years. Although the cost per admission and the length of stay (LOS) for HAP tended to be higher, the overall cost attributed to CAP was found to be greater, due to the greater prevalence of CAP.[5]

Data epidemiological findings of an association of high incidence of stroke associated pneumonia (SAP) with severe neurological deficits on admission and dysphagia in an stroke center unit (SCU) setting. As the optimal management strategy for SAP is still unclear, more clinical studies are needed to improve the strategies of prevention and treatment of SAP, especially in an acute ward setting. It may be necessary to develop an organized approach to evaluate SAP for better management of acute stroke.[14]

RISK FACTORS AND COMORBIDITY OF PNEUMONIA

Risk factors for CAP in populations all over the world, and decreased host immune system are the biggest factors associated with CAP. Factors of aging, smoking (active and passive), underlying comorbid circumstances, including chronic cardiorespiratory conditions, kidney and liver, and no less important is the presence of HIV infection is a common risk factor. Risk factors for community-acquired pneumonia include the following: (i) extremes of age (very young and the aging), (ii) male gender, (iii) certain populations (various racial or ethnic groups), (iv) lifestyle factors (excessive alcohol consumption and smoking), (v) underlying comorbid conditions such as (a) chronic cardiorespiratory illnesses, (b) chronic renal disorders, (c) hepatic conditions, (d) diabetes mellitus, (e) neoplastic diseases, (f) human immunodeficiency virus infection, (vi) medications (e.g., inhaled corticosteroids, proton pump inhibitors), (vii) additional risk factors associated with pneumococcal infections in particular (e.g., myeloma, hypogammaglobulinemia (such as IgG2 deficiency), surgical asplenia, or "functional" asplenia (such as in sickle cell disease)[13], and stroke (neurological deficits on admission and dysphagia (SAP).[14] The prevalence of larger and often

risky comorbidities for CAP and HAP is lung disease, cardiovascular disease, and diabetes mellitus, and it were more frequent in the older age groups.[5]

PREVENTION OF PNEUMONIA

There are many forms of pneumonia that can be caused by bacteria, viruses and, more rarely, fungi. *S. pneumonia* is the most common cause of pneumonia.[15] Despite some forms of pneumonia being potentially preventable through vaccination, surveys suggest that only between 20 - 30% of adults aged 65 years and over,[16] despite the age group of 65 years or older generally decreases the immune system, and has an increased risk of pneumococcal disease.[17] Globally, vaccination of adults is poor. Adult pneumococcal vaccination is a vital 'healthy ageing' tool and one that all stakeholders from government to individuals must seek to utilise. This is particularly the case in resource-poor settings but, fortunately, there is a substantial impact to be gained in prevention of adult disease from the vaccination of children.[1]

Adult vaccination today is an underutilized public health strategy despite recommendations for vaccination. Pneumococcal vaccination is a simple way to help reduce the risk of pneumococcal pneumonia among at-risk groups, including the 65 years and over. However, the survey estimates that only between 20-30% of adults aged 65 and above are currently vaccinated.[16] Vaccination of HIV infected adults to prevent invasive pneumococcal disease was a success using conjugate vaccine but failed using polysaccharide vaccine.[1]

The high morbidity and mortality of pneumonia in old age suggests that prevention is important. Delay in diagnosis due to less typical symptoms and signs of pneumonia in old age adds attention to the importance of preventing pneumonia. Influenza infection and pneumonia degrade the quality of life of elderly people, where functional status decreases during infection and recovery. Increased antibiotic resistance also complicates treatment, reduces quality of life and causes high mortality.[4]

Influenza is a major cause of morbidity and mortality among older adults in the United States, who may also have chronic medical conditions that place them at high risk for complications from influenza. It is recommended that influenza vaccination in adults> 65 years and people with chronic diseases.[18] However, despite the safe and effective vaccines, long-term vaccination recommendations have not been optimal. Studies have shown that coverage of influenza vaccination among adults. Until now the vaccination of people aged> 65 years in the united states has not 90 percent, coverage until 2013 only reached 65%.[18]

Factors contributing to vaccination coverage are how to implement vaccination programs, differences in delivery infrastructure, differences in the effectiveness of specific interventions implemented by other stakeholders (ie community campaigns, health care provider-based strategies and vaccinations in the workplace); and differences in population attitudes toward influenza and influenza vaccinations. Influenza vaccination can help older adults maintain health and quality of life by minimizing the most severe outcomes from influenza, which occur at higher rates among adults ≥65 y. New approaches are needed to enhance vaccine uptake in this age group. The 2013 National Vaccine Advisory Committee (NVAC) revised Standards for Adult Immunization Practice call on all healthcare professionals to ensure adult patients are vaccinated by assessing vaccination status of all patients, strongly recommending necessary vaccinations, administering vaccinations or referring patients for vaccinations, and documenting vaccinations.[18]

PNEUMONIA IN INDONESIA

In many countries outside Indonesia, many and easy to obtain epidemiological data, prevalence, etiology, diagnosis and prevention of pneumonia, not so in Indonesia. The data as above are national-scale is very difficult to get it.[19] Nevertheless we present data of pneumonia in Indonesia. A sentinel hospitals research for incidence of influenza-associated severe acute respiratory infections (SARI) in three districts of Indonesia (Gunung Kidul, Balikpapan, Deli Serdang), and found 14% influenza-positive SARI cases (27 of 170 patients) aged >14 years. Only 2% influenza cases reported having influenza vaccination in the last 12 months, all were aged ≥50 years old. At this site, observed incidence among those ≥60 years was higher than that among younger adults (15-59 years), but lower than that among children aged <15 years. The combined incidence of influenza-associated SARI varied during 3 years, ranging between 13 and 19 per 100 000 population, with an increase in the point estimate each year. Among the three hospitals, the influenza-associated SARI incidence was highest in children aged 0-4 years (82-114 per 100 000 population) followed by those aged 5-14 years (22-36 per 100 000 population).[20]

The prevalence of pneumonia in acute geriatric ward of Cipto Mangunkusumo Hospital in 2000 was 54.8% with death rate of 32.5%, a year later (2001) the prevalence increased to 61.6% with a mortality rate of 32.9%.[21] In 2003, the prevalence of pneumonia in geriatric patients decreased to 52.2%, with a high mortality rate of 30.3%.[22] Pneumonia patient age between 44-88 years, age> 60 years 32%.[11] In elderly pneumonia Mean age 68,44 years old, age> 80 years 6,6% (Elsa F Sari, 2016). In SAP mean age 58.4 +10.1 years (Ita M Sari, 16). In the SARI study (all age studied) age> 60 years 3%.[20] CAP RSCM median age 58 years (18-89), age> 65 years 35.9%.[23] Gram positive 24.1%; 56% GNB. Gram-positive pathogens were Staphylococcus epidermidis (8.7%) and Streptococcus viridian 7.3%. The highest GNB was K. pneumonia (28%) followed by Acinetobacter spp. 10% da Pseudomonas spp. 10%.[23]

In study of Farida et al.,[11] A single causative agent viruses and bacteria, polymicrobial causative including viral infections superimposed with bacterial infection (multiple viruses, multiple bacteria, and ombinations of virus(es) and bacteria). Viruses were identified in 45% patients, with influenza A as commonest (13.5%) and influenza B 4.5%. All influenza A viruses were H3N2. Together, influenza A and B viruses caused cases of CAP as single or as co-pathogen. found most bacteria causing CAP were susceptible to early generation antibiotics. Research conducted by Sari et al[24] at RSCM Jakarta on 106 elderly patients (> 65 years) found that 3 factors related to diagnosis of pneumonia are cough, ronchi, and infiltrate. CRP which is usually a marker of acute inflammation is not found in this study. The most common comorbidities are congestive heart failure followed by diabetes mellitus and cerebrovascular disease.

Severe pneumonia (PSI IV-V) was found in CAP (44%) patients. Most (70%) chest X-rays show bronchopneumonia. Climate, age difference, underlying disease, and the type of pneumonia that may cause the etiology of CAP (bronchopneumonia) in Farida et al.[11] In SARI-influenza study the underlying diseases of the patients were asthma, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease, chronic kidney disease, and hematology disorder.[20] Many comorbidities in other study in CAP including hypertension, diabetes mellitus, chronic heart failure, chronic kidney disease, maliganancy, cerebrovascular disease, liver cirrhosis, acquired immunodeficiency syndrome, and COPD.[23] Fifty-two percent of patients have an underlying disease, 19% have two or more underlying diseases.[11]

Regarding antibiotics consumed before the hospital, only 15% of patients had received oral antibiotics prior to hospital admission, while 50% were unsure whether they had received antibiotics or not.[11] Appropriateness of Antibiotic Usage Gyssens criteria for pneumonia in the predictor mortality CAP study at RSCM Jakarta, was appropriate 65.2%, very long administration 11.8%, alternative more effective 16.1%, alternative narrower spectrum 4.8%.[23]

For mortality, Farida H et al., identified no significant difference in underlying diseases, PSI class, length of stay, and mortality among patients with single viral, single bacterial, and mixed viral-bacterial infections ($P>0.05$). The overall 30-day mortality rate was high (30%) and significantly associated with severity of disease ($P<0.001$). The mortality rate ranged from 17% in PSI class I patients to 80% in PSI class V patients. Interestingly, survival analysis showed a significantly lower survival rate in patients with unknown etiology. Hospitalization mortality of CAP was 23.9%, similar with others early study at RSCM Jakarta. The high mortality of CAP patients at RSCM cause of many patients with severe comorbidity disease, severe pneumonia, and no appropriate empirical antibiotics.[23]

Early death (<48 hours of hospitalization) happened in 18 patients (41% mortality), and was associated with respiratory failure or irreversible septic shock; most of the early deceased patients (14 subjects) had delayed or no access to ICU care because of limited availability of the service. Late death (>48 hours of hospitalization) occured in 14 patients (32% of mortality), and was associated with worsening conditions from CAP (7 patients) or with their underlying diseases (7 patients). Despite clinical improvement, 12 patients (27% of mortality) died after discharge from hospital for in-home recovery within 30 days of admission. The circumstance of these latter death remained unknown.[11]

A retrospective cohort study was performed on adult CAP hospitalized RSCM admissions during 2010-2014. Clinical and laboratory data along with outbound status (life or death) during treatment were obtained from the medical record, the result was 434 CAP patients. Mortality during treatment was 23.9%. The median age of the patient was 58 (18-89) years and the median duration of treatment was 8 (1-63) days. The most common pathogens from sputum cultures are Klebsiella pneumoniae (28%), and the predictors of mortality are severe pneumonia, sepsis, respiratory failure, CCI> 5, and albumin <3 g / dl.[23]

The number of elderly people in Indonesia increases and will reach the highest acceleration in the world by 2020, ie 41.4% compared to the level in 1996. By 2025, there will be 25.5 million octogenarians due to longer life

expectancy. Increasing numbers of elderly require greater attention and health care as they are more susceptible to many acute illnesses. One of the diseases includes respiratory tract infections, which is the leading cause of death.[4] Unfortunately no data in Indonesia regarding adult vaccination of influenza and pneumonia.

In 2012 The Indonesian Society of Medical Gerontology produces a consensus that Indonesia's elderly population get influenza and pneumonia immunization. This consensus is structured for the elderly population of Indonesia to receive influenza and pneumonia immunization. It is expected that by 2025: 60% of Indonesia's elderly population will get influenza immunization every year and by 2025: 50% of the elderly population of Indonesia will receive pneumonia immunization.[4]

The use of extensive influenza vaccinations in other parts of the world can help explain the differences in influenza incidence in CAP. CAP management guidelines interpreted and applied in Europe, North America, and Australia may not be directly applicable in Indonesia.[11] Pathogens etiology of pneumonia is difference in Indonesia and other part of the world.

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