Community Acquired Pneumonia - A Malaysian Perspective

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Introduction

Community acquired pneumonia (CAP) is a common illness and potentially life threatening especially in older adults and those with co-morbid disease. It is a major cause of morbidity and death worldwide. Recognising the clinical importance of CAP, many countries have developed national guidelines for the management of this condition[1,2,3,4,5,6,7]. In Malaysia, the Malaysian Thoracic Society together with the Ministry of Health and the Academy of Medicine, Malaysia are developing guidelines for the management of CAP in adults.

The microbial aetiology of community acquired pneumonia

Although many microorganisms have been associated with CAP, it is a small range of key pathogens that cause most cases. *Streptococcus pneumoniae* (pneumococcus) is the most frequently identified pathogen, with the highest incidence of this organism reported in studies that used urinary antigen detection. Apart from *Streptococcus pneumoniae*, a great deal of literature in Western countries has reported *Haemophilus influenzae*, atypical pathogens – *Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila* and viruses (influenza virus, adenovirus, respiratory syncytial virus, parainfluenza virus, coronavirus) as the common pathogens of CAP[3,7,8,9,10,11]. Gram-negative bacilli (*Enterobacteriaceae* and pseudomonadas) are the cause of CAP in patients who have had previous antimicrobial treatment or who have pulmonary comorbidities)[12]. In one study, 33% of hospitalized CAP patients with unknown aetiology diagnosed by routine methods were found to due to *Streptococcus pneumoniae* based on findings from transthoracic needle lung aspiration, suggesting that many patients without a known pathogen have pneumococcal infection[13].

The microbial aetiological distribution of CAP reported in the literature depends on the patient population, the geographical region, the intensity of investigations carried out and the occurrence of epidemics of infection. Even when carefully sought for in large prospective studies, the putative causative organism remains unknown in about half of all patients with CAP. In an observational study that assessed the 'real-world' practice from several centres in the USA, only 6% of outpatients and a quarter of inpatients with CAP had the cause of their disease defined[14]. Reasons for failure to identify the aetiological agent include prior treatment with antibiotics, unusual pathogens that go unrecognized, viral infections, non-infectious mimic of CAP, and pathogens that are currently not identified or recognized.

The microbial aetiology of community acquired pneumonia in patients requiring hospitalisation

The results of some studies on CAP requiring hospitalization from United Kingdom, the remainder of Europe, Australia and New Zealand, North America and Asia are compared in Table I. The aetiology of CAP in Japan and Korea does not differ markedly when compared with that of Western countries except for the low incidence of *Legionella* pneumonia[15, 16, 17]. The low incidence of Legionella pneumonia is also found in the other Asian countries which could have been due to limitations of laboratory tests used. The epidemiologic data from Bangkok[16] indicate that the microbial agents causing CAP in Thailand, in general, are not different from those in Western countries.

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In the Japanese series, *Chlamydia pneumoniae* was identified in 3%[15] and 7.5%[20] of the cases, respectively. In the AsiACAP study[25] which was conducted from October 2001 – December 2002 in 12 urban tertiary medical centres in Asia (Beijing, Shanghai, Seoul, Taipei, Hong Kong, Bangkok, Manila, Kuala Lumpur, Petaling Jaya and Jakarta involving 1756 out- and in-patients aged 2 years and above, paired sera (acute and convalescent) were obtained from 1374 patients (78.2%) [children up to 15 years (448 patients), adults (from age 15 years and above) (926 patients)]. Infection rates based on ≥4-fold rise in antibody titre between acute and convalescent sera were found to be 9.4% for *Mycoplasma pneumoniae*, 4.3% for *Chlamydia pneumoniae* and 6.2% for *Legionella pneumophila*. The overall infection rate for atypical pathogens is 19.9%.

A number of studies in Asia where the prevalence of tuberculosis is high have shown that infection due to *Mycobacterium tuberculosis* may commonly present as an apparent CAP[18,21,23,24]. In a study conducted in Argentina, *Mycobacterium tuberculosis* was identified in 2.8% of 253 patients with moderate CAP[26]. One [22] of the Malaysian studies excluded patients with tuberculosis while in the other two studies, tuberculosis accounted for 15.3% and 4.8% of the cases, respectively[23,24]. Although pulmonary tuberculosis is a chronic respiratory infection, it can present as CAP and it should be a differential diagnosis in areas where tuberculosis is endemic.

In studies conducted in Malaysia, 2 out of 127 (1.6%) patients in the Kuala Lumpur series had melioidosis;[22] while *Burkholderia pseudomallei* was not isolated in any patient in the Penang series[23]. In the Bangkok study,[20] *Burkholderia pseudomallei* was identified in 1.4% of the cases. However, in rural Northeastern Thailand, *Burkholderia pseudomallei* was identified in 15.4% of the patients hospitalised for CAP[19]. *Burkholderia pseudomallei* should be considered a causative organism in patients with CAP in rural Southeast Asia particularly if the patient has diabetes mellitus[19].

Studies performed in the Asia Pacific region showed that Gram-negative bacilli other than *Haemophilus influenzae* such as *Klebsiella pneumoniae* are more frequently isolated[15,17,19,20,22,23,24]. The differences in the microbiology of CAP as compared to what is reported in the West must be taken into consideration when selecting the appropriate antibiotics for initial empirical therapy of CAP in this region.

The microbial aetiology of severe community acquired pneumonia

There is no standard definition for diagnosing severe CAP. In treatment guidelines developed in the West, patients with CAP admitted to an intensive care unit (ICU) are considered as having the severe form of the disease. However, policies for ICU admission may vary considerably between medical centres. Patients not admitted to an ICU could also be having severe CAP. Host-factors such as underlying diseases, can influence severity of presentation of CAP. Severe CAP accounts for approximately 5-35% of hospital-treated cases of pneumonia with the majority of patients having underlying comorbidities.

The American Thoracic Society proposed defining severe CAP on the presence of one major criteria or 2 minor criteria[6]. The major criteria consist of the need for mechanical ventilation and septic shock while the minor criteria include chest radiograph showing bilateral or multilobe involvement, a PaO_2/fraction of inspired oxygen (FiO_2) ratio less than 250 mm Hg and systolic blood pressure of 90 mm Hg or less. The microbiology of severe CAP patients requiring ICU admission in various studies are shown in Table II.

The microbiology of severe CAP in patients admitted to intensive care units is similar to that in other patients admitted to hospital with CAP. Studies conducted in the west show that *Streptococcus pneumoniae* to be the most frequent causative microorganism associated with severe CAP and it is detected in about 20% of cases. Other frequently identified pathogens are *Haemophilus influenzae*, gram-negative enteric bacilli and *Staphylococcus aureus* (although few of these cases could be judged as definite, i.e. confirmed bacteraemia or isolation from pleural fluid or lung tissue); and *Legionella pneumophila*[7,26,27]. A review of nine studies of CAP that resulted in admission to an ICU (seven from Europe and one each from USA and South Africa) noted that *Legionella spp* were the second most commonly identified pathogens[30]. In an international collaborative survey of 508 patients with culture-positive legionellosis, 92% of the isolates with serogroup 1 were *L pneumophila*, accounting for 84% of the total. *L pneumophila* serogroup 1 accounted for 88% of isolates in America and Europe but for only 46% in Australia and New Zealand where *L longbeachae* accounted for 30% of cases[31]. In 2 studies on severe CAP conducted in Singapore, *Legionella spp* was not identified in any of the patients[28,29]. However, *Burkholderia pseudomallei* was a common causative

organism identified (Table II). Melloidosis should be considered a diagnostic possibility especially if the patient has diabetes mellitus. Pseudomonas aeruginosa should be considered in patients with underlying structural lung disease, for example in patients with bronchiectasis or chronic obstructive pulmonary disease. Apart from these pathogens, other pathogens associated with severe CAP are also frequently isolated from patients with non-severe CAP.

The microbial aetiology of community acquired pneumonia in patients treated on an ambulatory basis

The most common pathogens identified from recent studies of mild (i.e. in ambulatory patients) CAP are *Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydia spp*, and viruses (mostly influenza virus) (Table III)[8,20,26,32,33]. In one study, *Mycoplasma pneumoniae* is the most common pathogen in patients younger than 50 years and without important comorbid conditions, whereas *Streptococcus pneumoniae* is the most common pathogen for older patients or those with significant underlying disease[34]. The high infection rates caused by *Chlamydia pneumoniae* (36.7%) and Mycoplasma pneumoniae (29.6%) in ambulatory patients in the Bangkok study[20] could be explained by many factors. First, paired sera collected from most the patients for the diagnosis of atypical pathogens in the study probably improved the diagnostic yield. Second, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* often cause a mild clinical disease, therefore patients are more likely to be seen as outpatients. Moreover, the infection by the atypical microorganisms is more common among persons in a younger age group, as was seen in the outpatients.

Initial site and antibiotic for empirical treatment

The selection of the initial site of treatment and the initial empirical antibiotic therapy is based on (1) risk stratification of the patient according to (a) the presence of co-morbid conditions; (b) the severity of the pneumonia at presentation (based on ' physical findings, chest radiograph changes and laboratory findings); and (c) the presence of identified clinical risk factors for drug-resistant and unusual pathogens ; and (2) the local epidemiology and resistance pattern. Both the 2001 American Thoracic Society[6] and the 2000 Infectious Disease Society of America[3] guidelines indicate that age alone is not a reason for hospitalization. Studies have shown that age alone, in the absence of comorbid illness, has little impact on the bacterial etiology of CAP[35-37].

Practice guidelines usually categorise CAP patients based on the site of treatment (outpatient, general ward, or intensive care unit), the presence of co-morbidity and modifying factors (e.g., risk for penicillin-resistant *Streptococcus pneumoniae*)[1,2,3,4,5,6]. Each patient group is assigned a list of likely pathogens and suggested antimicrobial therapy. Guidelines advocate the use of those antimicrobials that provide coverage of both the likely pathogens and resistant strains.

Determining the initial site of treatment

Most patients with CAP can be safely treated as outpatients. However, about 20% of CAP patients need hospitalization and approximately 1% require treatment in an ICU[38,39]. Patients should be admitted if they require close observation, intravenous antibiotics, respiratory support, or there are other concerns. Risk factors for increased mortality associated with CAP include extremes of age; comorbid conditions such as malignant disease, congestive cardiac failure, coronary artery disease and alcoholism; vital sign abnormalities; and certain laboratory and chest radiographic findings[40]. The decision whether or not to admit a patient depends on the clinician's judgment which is an "art of medicine". However, prognostic scoring rules are available which provide support for this decision[7,41,42]. A pneumonia severity index (PSI) score or the "pneumonia prediction rule", has been developed from studies of the pneumonia Patient Outcomes Research Team (PORT)[41]. This prediction rule or index can be used to stratify patients to one of five risk categories with a score or point system based on 7 laboratory and chest radiographic parameters after an initial evaluation of three factors: age (younger than 50 years or 50 years or older), presence of 5 comorbid conditions (neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease and renal disease), and mental status and vital signs on admission. This method has been validated for identifying patients at risk of dying within 30 days. The risk of death is low for risk classes I-III (0.1-2.8%), intermediate for class IV (8.2-9.3%), and high for class V (27-31%). Apart from being an effective method for triaging patients, this method is particularly useful for identifying low-risk patients who may be safely treated as outpatients[43-46]. Before calculating the severity index score, patients should be assessed for any pre-existing condition that may compromise the safety of home care, which includes haemodynamic instability, acute hypoxaemia, active comorbid conditions that warrant hospital admission, social or psychiatric problems

compromising home care, or the inability to take medication orally[47].

North American practice guidelines advocate the use of PSI as an objective measure of risk stratification to help determine the initial site of CAP treatment[3,5]. Easy-to-use versions of the PSI are now available on handheld computers and the Internet: http://ursa.kcom.edu/CAPcalc/default.htm, *http://ncemi.org* and http://www.emedhome.com/dbase.cfm.

Mortality prediction rules should be used to support, but not replace, clinician decision making. Whether or not a patient is admitted has an effect on the extent of diagnostic evaluation and the choice of empirical antibiotic therapy.

Mortality from CAP

The mortality from CAP in patients treated as out-patients is less than 1%, while that for hospitalised patients as a whole is 13.7%, in elderly patients 17.6%, patients with bacteraemia 19.6%, and patients admitted to ICU 36.5%[40]. In a recent study conducted in Malaysia (unpublished data), the overall in-hospital mortality rate in adult patients hospitalised for CAP was 11.1% while that for patients aged 30 years or younger was 0%, for patients aged 31 to 64 years was 7%, for patients aged 65 to 80 years was 12% and for patients aged 81 years and older was 41%[24]. The clinical features independently associated with an increased risk of dying from CAP in these patients were age older than 50 years, co-existing congestive cardiac failure, multilobar pneumonia, tachycardia of 125/min or more on admission, admission serum creatinine greater than 130 μmol/L, and acute respiratory failure.

Initial empirical antibiotic therapy for CAP

In most instances, a quick microbiological diagnosis is not possible and the microbial aetiology of CAP is unknown. As the microbial aetiology cannot be reliably predicted from the clinical, laboratory and radiological features, initial antibiotic treatment has to be empirical[48-50]. An awareness of the likely causative organism of CAP treated in different settings is important to allow the start of appropriate empirical antimicrobial treatment. Table IV shows the most common pathogens associated with CAP as derived from collective results of various studies conducted in the west and in the Asia Pacific region[7,8,12,13,15-29,32,33].

North American and European guidelines[3,4,6,7] recommend initial empirical therapy consisting of a macrolide combined with a broad-spectrum beta-lactam antibiotic or monotherapy with a newer fluoroquinolone which has antipneumococcal activity ("respiratory fluoquinolone") in all CAP patients requiring hospitalisation. Retrospective large population studies have found that combinations of beta-lactam antibiotics plus macrolides or monotherapy with respiratory fluoroquinolones, as initial therapy for non-severe CAP, reduce length of stay and mortality, even when *Streptococcus pneumoniae* is the causative microorganism[51-56]. These favorable outcomes may be explained by the role of atypical pathogens as aetiological agents of CAP, the anti-inflammatory effects of macrolides or resistance to beta-lactam antibiotics of the most important pathogens. The respiratory fluoroquinolones can also be used to treat severe CAP[57,58]. Finch *et al*[58] showed moxifloxacin to have better clinical and bacteriological success when compared with co-amoxiclav with or without a macrolide in the treatment of patients hospitalised with CAP and severe CAP. However, the development of resistance to these respiratory fluoroquinolones has already been reported[59,60]. Despite a high level of activity against *Streptococcus pneumoniae* and atypical organisms, fluoroquinolones, are not advocated by the Centers for Disease Control (CDC) Drug-Resistant *Streptoococcus pneumoniae* Therapeutic Working Group (DRSPTWG) because of their overextended spectrum of coverage (inclusive of gram negative bacteria) and concern about the emergence of resistant *Streptococcus pneumoniae*. The use of a third-generation cephalosporin and a macrolide antibiotic provides a more appropriate spectrum of coverage for CAP without carrying the added risk not only of resistant *Streptococcus pneumoniae* but also of the emergence of many resistant gram-negative organisms that have nothing to do with the patient's pneumonia. The DRSPTWG recommends reserving the use of fluoroquinolones for patients who are allergic to first-line agents, in whom first-line therapy has failed, or who have proven resistance to penicillin[2].

CAP caused by penicillin resistant *Streptococcus pneumoniae* (minimum inhibitory concentration less than 4 μg/ml), can still be adequately treated with beta-lactams at the right dosage[61]. The proposed initial empirical antibiotic therapy of bacterial CAP in immunocompetent adults according to the treatment setting in Malaysia is shown in Table V.

Empirical antibiotic therapy for hospitalized non-severe community acquired pneumonia

Antibiotic therapy should be initiated promptly as this is associated with better outcomes[62,63]. Antibiotic therapy should cover for *Streptococcus pneumoniae* and atypical pathogens which have been shown to be prevalent as causative agents. The antibiotic options include:

- A macrolide plus a penicillin or second generation cephalosporin or a non-pseudomonal third generation cephalosporin
- A macrolide plus a ß-lactam / ß-lactamase inhibitor
- Monotherapy with a fluoroquinolone with enhanced antipneumococcal activity.

Epidemiological clues that may lead to diagnostic considerations are listed in Table VI[3]. In patients with the following co-morbidities:

- COPD – antibiotic treatment should cover for *Haemophilus influenzae* and *Moraxella catarrhalis*.
- Bronchiectasis – antibiotic treatment should cover for *Pseudomonas aeroginosa*. Examples of antibiotic regimens – a ß-lactam plus an aminoglycoside or a ß-lactam plus ciprofloxacin
- Patients on long-term corticosteroids (dose exceeding 10 mg/day of prednisolone) - should cover for *Pseudomonas aeroginosa*

Empirical antibiotic therapy for severe community acquired pneumonia

Since Streptococcus pneumoniae is the most frequently identified pathogen in severe CAP and *Legionella pneumophila* is feared for the potential severity of infection empirical antibiotic therapy should cover for these two pathogens[64]. The early and rapid initiation of empiric antibiotic treatment is critical for a favorable outcome. It should include an intravenous beta-lactam together with either a macrolide or a fluoroquinolone. Modifications of this basic regimen should be considered in the presence of distinct comorbid conditions and risk factors for specific pathogens. For example, empirical therapy for *Pseudomonas aeruginosa* is recommended if the patient has bronchiectasis and antibiotic cover for *Burholderia pseudomallei* should be considered if the patient has diabetes mellitus. Failure to define a pathogen in patients with severe CAP has not been associated with a different outcome than if a pathogen is identified[39,65].

Pathogen-specific therapy

If a specific pathogen can be identified within 24-72 hours then continued treatment can be guided by this information. For example, if penicillin-susceptible *Streptococcus pneumoniae* is isolated, treatment should be modified by selecting a narrow spectrum antibiotic (such as penicillin or amoxicillin), which will help to reduce the selective pressure for resistance. This information is often available at the time of switching from parenteral to oral therapy.

Duration of antibiotic therapy

Most experts recommend the total duration of antibiotic therapy should be 10-14 days, depending on the severity of the pneumonia and the response to therapy[66]. An extended course of intravenous antibiotics is generally recommended for bacteraemia due to high-risk organisms (*Staphylococcus aureus* or gram-negative bacilli) or suppurative complications[67]. Antibiotic treatment for 21 days has been recommended for infection due to *Legionella pneumophila*. The American Thoracic Society recommends that patients switched to oral antibiotics can be discharged on the same day if other medical and psychosocial factors permit[6]. Evidence from observational studies suggests that there is no need to observe patients for 24 hours after a switch from intravenous to oral therapy[67,68].

Susceptibility of *Streptococcus pneumoniae* to commonly used antimicrobial agents stratified by susceptibility to penicillin

In-vitro activities of 6 antibiotics against 92 strains of *Streptococcus pneumoniae* isolated from patients in Malaysia is shown in Table VII[69]. The data is from a study conducted between 1996 – 1997. Specimens were referred by laboratories in hospitals throughout the country to bacteriology departments at the Institute for Medical Research and the University of Malaya Medical Centre. 61.9% of the strains were isolated from respiratory tract specimens. Minimum inhibitory concentrations (MICs) were determined by the Etest method. Ten (10.9%) isolates, all from respiratory tract specimens, were non-susceptible to penicillin (5 exhibiting intermediate susceptibility and another 5 resistance). The most active drug was co-amoxiclav (96.8% of isolates, including 2 that were resistant to penicillin being susceptible) followed by ceftriaxone, cefuroxime and azithromycin. As the MIC breakpoint for susceptibility to cefaclor has not been recommended by United States National Committee for Clinical Laboratory Standards (NCCLS), the percentage of isolates susceptible to this agent could not be calculated. Of the 6 strains resistant to ceftriaxone, 5 were resistant to penicillin and one exhibited

intermediate susceptibility. Of the 7 strains that were resistant to cefuroxime, 5 and 2 isolates, respectively, were resistant and intermediately susceptible to penicillin. Twelve strains were resistant to azithromycin and 7 of these exhibited reduced susceptibility to penicillin.

Penicillin-resistant *Streptococcus pneumoniae*

The risk factors for penicillin-resistant *Streptococcus pneumoniae* (PRSP) include age younger than 2 years or older than 65 years, beta-lactam antibiotic treatment within the past 3 months, alcoholism, multiple medical comorbidities, immunosuppressive illness or treatment, and exposure to a child in a day-care centre[70,71]. Several studies showed that age older than 65 years is, by itself, a specific epidemiological risk for CAP due to PRSP, but is not an independent risk factor for other organisms[71,72].

Under the former NCCLS criteria, *Streptococcus pneumoniae* infections treated with beta-lactam antibiotics to which isolates had intermediate resistance were associated with worse clinical outcomes for meningitis but not for pneumonia. This difference might be related to the attainable concentrations of beta-lactam antibiotics in cerebrospinal fluid (CSF), compared with plasma and interstitial fluid. Beta-lactam antibiotic concentrations in the lung interstitia are similar to those measured simultaneously in serum, and levels in CSF are lower than those in serum[73]. The presence of penicillin resistance itself has not been shown to adversely affect outcome in CAP treatment unless penicillin MIC vales are 4 mg/mL or higher[3,74]. As of January 2002, the NCCLS increased the MIC breakpoints for cefotaxime and ceftriaxone. Isolates with MICs of $\leq$1 μg/mL are now considered susceptible, those with MICs of 2 μg/mL are intermediate, and those with MICs of $\geq$4 μg/mL are resistant. The new breakpoints apply to non-meningeal *Streptococcus pneumoniae* infections and such infections by strains formerly considered to be intermediately susceptible and even some that were regarded as resistant can be treated successfully with the usual doses of beta-lactam antibiotics.

Antibiotic options in the treatment of penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae* are shown in Table VIII. For patients admitted to the general ward, high-dose benzylpenicillin should be adequate, as long as the MICs of isolates in the local community is <2 μg/mL. Alternatively, ceftriaxone or cefotaxime (not available in Malaysia) can be used for strains of pneumococcus with an MIC of <2 μg/mL[4]. If the patient has a history of anaphylactic allergic reaction to penicillin or is allergic to cephalosporins, intravenous vancomycin or an antipneumococcal fluoroquinolone are acceptable substitutes. Current guidelines for treating PRSP pneumonia recommend choosing one of the following antibiotics based on susceptibility testing results: ceftriaxone, cefotaxime, antipneumococcal fluoroquinolones, or, if the isolate is resistant to fluoroquinolone and cephalosporin, vancomycin[4].

Treatment guidelines cannot capture every clinical situation and it is therefore the responsibility of the clinician to balance the history and clinical features, assess the importance of risk factors and interpret local epidemiology and laboratory data in order to make the best judgement for an individual patient.

Table I: Microbiology of community acquired pneumonia in patients requiring hospitalisation

Location	No. of patients	Frequency / Rank order of microbial cause (%)						
		1	2	3	4	5	6	Unknown
United Kingdom[7] (5 studies)	1137 (mean %)	*S pneumoniae* 39	*C pneumoniae* 13.1	*M pneumoniae* 10.8	*Influenza A & B* 10.7	*H influenzae* 5.2	*Legionella spp* 3.6	30.8
Other parts of Europe[7] (23 studies)	6026 (mean %)	*S pneumoniae* 19.4	*C pneumoniae* 6.3	*M pneumoniae* 6	*Influenza A & B* 5.3	*Legionella spp* 5.1	Gram negative enteric bacilli 3.3	50.7
Australia & New Zealand[7] (3 studies)	453 (mean %)	*S pneumoniae* 38.4	*M pneumoniae* 14.6	*H influenzae* 9.5	*Legionella spp* 7.5	Gram negative enteric bacilli 4.6	*C pneumoniae* 3.1	31.6
North America[7] (4 studies)	1306 (mean %)	*S pneumoniae* 11.3	*H influenzae* 6.3	*C pneumoniae* 5.9	*Influenza A & B* 5.9	Gram negative enteric bacilli 5.3	*Legionella spp* 4.8	40.7
Okayama[15]	318 (326 episodes)	*S pneumoniae* 23	*H influenzae* 7.4	*M pneumoniae* 4.9	*K pneumoniae* 4.3	*S milleri* 3.7	*C pneumoniae* 3.4	39
Okayama[16]	200	*S pneumoniae* 20.5	*H influenzae* 11.0	*M pneumoniae* 9.5	*C pneumoniae* 7.5	*S aureus* 5.0	Anaerobes 4.0	41.5
Korea[17]	562 (588 cases)	*S pneumoniae* 21.7	*K pneumoniae* 14.8	*Ps aeruginosa* 9.8	*S aureus* 9.5	*Streptococcus viridans* 5.7	*Enterobacter cloacae* 4.2	61.7
Hong Kong[18]	90	*M tuberculosis* 12	*S pneumoniae* 12	*Chlamydia spp* 6	Viral 6	*H influenzae* 4	*M pneumoniae* 3	59
Khon Kaen[19]	230	*S pneumoniae* 23.1	*K pneumoniae* 19.2	*B pseudomallei* 15.4	*H influenzae* 11.5	*M pneumoniae* 6.2	*S aureus* 4.6	47.8
Bangkok[20] (TB cases were excluded)	147	*S pneumoniae* 22.4	*Chlamydia pneumoniae* 16.3	*K. pneumoniae* 9.5	*M. pneumoniae* 6.8	*L pneumophila* 5.4	*H influenzae* 2.7	29

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Location	No. of patients	Frequency / Rank order of microbial cause (%)						
		1	2	3	4	5	6	Unknown
Singapore[21]	96	*M tuberculosis* 21	*S pneumoniae* 12	Gram negative bacilli 10	*H influenzae* 5.2	*M pneumoniae* 5.2	*S aureus* 4.2	42
K. Lumpur[22] (For atypical pathogens: only serology for Mycoplasma was done)	127	*K pneumoniae* 10.2	*S pneumoniae* 5.5	*H influenzae* 5.5	*M pneumoniae* 3.9	*Ps aeruginosa* 3.9	*Burkholderia pseudomallei* 1.6	58.3
Penang[23] (For atypical pathogens: serology for Mycoplasma and Legionella was done)	98	*M tuberculosis* 15.3	*K pneumoniae* 7.2	*Ps aeruginosa* 6.1	*S aureus* 5.0	*S pneumoniae* 3.0	*Acinetobacter spp* 3.0	57.1
K. Lumpur[24] (unpublished data)	352	*K pneumoniae* 11.4	*M pneumoniae* 6.3	*M tuberculosis* 4.8	*S aureus* 3.7	*S pneumoniae* 3.4	*H influenzae* 3.1	59.1

Table II: Microbiology of severe community acquired pneumonia requiring ICU admission

Location	No. of patients	Frequency / Rank order of microbial cause (%)					
		1	2	3	4	5	Unknown
United Kingdom[7] (4 studies)	185 (mean %)	*S pneumoniae* 21.6	*Legionella spp* 17.8	Viruses 9.7	*Staph aureus* 8.7	Influenza A & B 5.4	32.4
Other parts of Europe[7] (10 studies)	1148 (mean %)	*S pneumoniae* 21.8	Gram- negative enteric bacilli 8.6	*Staph aureus* 7	*C pneumoniae* 6.6	*Legionella sp* 5.5	43.3
New York[27]	104 (all patients 75 years of age or older)	*S pneumoniae* 14	Gram- negative enteric bacilli 14	*Legionella sp* 9	*H influenzae* 7	*Staph aureus* 7	47
Argentina[26]	39	*S pneumoniae* 15.4	*C pneumoniae* 7.7	*Staph aureus* 5.1	*M pneumoniae* 5.1	*Legionella pneumophila* 5.1	41.0
Singapore[28]	59	*K. pneumoniae* 15	*H influenzae* 8	*Staph aureus* 7	*Burkholderia pseudomallei* 7	*S pneumoniae* 5	32
Singapore[29]	57	*Burkholderia pseudomallei* 18	*M tuberculosis* 16	*Klebsiella spp* 9	*Staph aureus* 9	*M pneumoniae* 7	28

Table III: Microbiology of community acquired pneumonia in patients treated on an ambulatory basis

Location	No. of patients	Frequency / Rank order of microbial cause (%)						
		1	2	3	4	5	6	Unknown
Lausanne[32]	170	*S pneumoniae* 22.9	*M pneumoniae* 14.1	Influenza virus 11.8	*C pneumoniae* 5.3	*Coxiella burnettii* 2.4	*H influenzae* 1.8	45.9
Finland[8]	169	*S pneumoniae* 37	*M pneumoniae* 14	*Chlamydiae* 9	Viruses 8	*H influenzae* 4	*Moraxella catarrhalis* 2	45
Argentina[26]	54 ('mild' CAP)	*S pneumoniae* 13.0	*M pneumoniae* 7.4	*C pneumoniae* 3.7	Influenza A virus 3.7	*Cryptococcus spp* 3.7	*H influenzae* 1.9	64.8
Nova Scotia[34]	149	*M pneumoniae* 22.8	*C pneumoniae* 10.7	*M pneumoniae* and *C pneumoniae* 3.4	*C burnettii* 2.7	Influenza A virus 2.7	Other 7.4	48.3
Bangkok[20]	98 (no study on viral aetiology)	*C pneumoniae* 36.7	*M pneumoniae* 29.6	*S pneumoniae* 13.3	*Legionella pneumoniae* 8.2	*H influenzae* 1.0	-	24.5

Table IV: Common causative organisms in community acquired pneumonia according to site of care (severity)[7,8,12,13,15-29,32,33]

Outpatient	Non-ICU inpatient	ICU
- *Streptococcus pneumoniae*	- *Streptococcus pneumoniae*	- *Streptococcus pneumoniae*
- *Mycoplasma pneumoniae*	- *Mycoplasma pneumoniae*	- *Legionella species*
- *Haemophilus influenzae*	- *Chlamydia pneumoniae*	- *Haemophilus influenzae*
- *Chlamydia pneumoniae*	- *Haemophilus influenzae*	- *Gram-negative bacilli (Pseudomonas aerugionsa, Klebsiella pneumoniae)*
- *Mycobacterium tuberculosis*	- *Klebsiella pneumoniae*	- *Staphylococcus aureus*
- respiratory viruses (Influenza A and B, adenovirus, respiratory syncytial virus, parainfluenza)	- *Mycobacterium tuberculosis*	- *Burkholderia pseudomallei*
	- *Staphylococcus aureus*	- *Mycobacterium tuberculosis*
	- *Burkholderia pseudomallei*	
	- *Legionella species*	
	- aspiration (anaerobes)	
	- respiratory viruses	

Table V: Proposed initial empirical antibiotic therapy of bacterial community acquired pneumonia in immunocompetent adults according to the treatment setting

Site of treatment	Common organisms	Preferred antibiotic treatment options
Out-Patient (mild CAP)	**Risk category I** No co-morbidity Should cover for • Streptococcus pneumoniae • Mycoplasma pneumoniae • *	**Risk category I** (a) No recent antibiotic therapy • Macrolide (erythromycin 500 mg QID x 10 days, azithromycin 500 mg OD x 3 days, or clarithromycin 500 mg BD x 10 days) (b) Recent antibiotic therapy • Advanced macrolide (azithromycin or clarithromycin) plus either (i) high dose amoxicillin or (ii) high dose amoxiicillin-clavulate Or • Antipneumococcal fluoroquinolone alone (moxifloxacin 400 mg OD, gatifloxacin 400 mg OD or levofloxacin 500 OD)
	Risk category II Presence of co-morbidity • As in risk category I • Haemophilus influenzae • *	**Risk category II** (a) No recent antibiotic therapy • Advanced macrolide Or • Antipneumococcal fluoroquinolone (b) Recent antibiotic therapy • Advanced macrolide plus either (i) high dose amoxicillin or (ii) high dose amoxiicillin-clavulate or (iii)2nd generation cephalosporin (cefuroxime or cefprozil) Or • Antipneumococcal fluoroquinolone alone

Site of treatment	Common organisms	Preferred antibiotic treatment options
General ward (moderate CAP)	**Risk category III** Should cover for • As in risk category I • *Klebsiella pneumoniae* • *Haemophilus influenzae* • *Legionella* • *Staphylococcus aureus* • Other Gram–negatve bacilli - *Enterobacter* - ***Escherichia coli*** • penicillin-resistant *Streptococcus pneumoniae* • *	**Risk category III** (a) No recent antibiotic therapy • Macrolide plus either (i) ceftriaxone 1 gm OD or (ii) cefuroxime 750 mg TDS or (iii) β-lactam/β-lactamase inhibitor (amoxicillin-clavulanate or ampicillin-sulbactam) Or • Antipneumococcal fluoroquinolone alone (b) Recent antibiotic therapy • same as in (a) (regimen selected depends on nature of recent antibiotic therapy) For treatment of penicillin-resistant *Streptococcus pneumoniae* refer to Table VIII
ICU/high dependency unit (severe CAP)	**Risk category IV** Should cover for • As in risk category I including PRSP • *Klebsiella pneumoniae* • *Haemophilus influenzae* • *Legionella* • *Pseudomonas aeruginosa* • * • *Staphylococcus aureus* • *Burkholderia pseudomallei*	**Risk category IV** (a) *Pseudomonas* infection is not an issue • (i) Ceftriaxone 1 gm BD or (ii) β-lactam/β-lactamase inhibitor plus either (i) macrolide or (ii) Antipneumococcal fluoroquinolone (b) *Pseudomonas* infection is an issue Either (I) an antipseudomonal agent (piperacillin, piperacillin-tazobactam, imipenem, meropenem or cefepime) *plus* ciprofloxacin Or (II) An antipseudomonal agent *plus* aminoglycoside *plus* either (i) antipneumococcal fluoroquinolone or (ii) macrolide Cloxacillin or vancomycin • High dose ceftazidime Or • Imipenem For treatment of penicillin-resistant *Streptococcus pneumoniae* refer to Table VIII

**Mycobacterium tuberculosis* should be considered in all risk categories
OD = once daily, BD = twice daily, TDS = thrice daily, QID = four times a day

Table VI: Epidemiological conditions related to specific pathogens[3]

Condition	Commonly encountered pathogen(s)
Alcoholism	*Streptococcus pneumoniae* and anaerobes
COPD and/or smoking	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Legionella species*
Nursing home residency	*Streptococcus pneumoniae*, gram-negative bacilli, *Haemophilus influenzae, Staphylococcus aureus*, anaerobes and *Chlamydia pneumoniae*
Poor dental hygiene	Anaerobes
Suspected large-volume aspiration	Anaerobes, gram-negative enteric bacilli
Bronchiectasis	*Pseudomonas aeruginosa, Pseudomonas cepacia, Staphylococcus aureus*
Intravenous drug abuse	*Staphylococcus aureus*, anaerobes, *Mycobacterium tuberculosis* and *Streptococcus pneumoniae*
Diabetes mellitus	*Mycobacterium tuberculosis, Bukholderia pseudomallei*

Table VII: In-vitro activities of 6 antibiotics against 92 strains of *Streptococcus pneumoniae* isolated from patients in Malaysia[69]

Antibiotic	MICs (mg/L)		
	MIC_{90}	Range of MICs	Susceptible isolates (%)*
Co-amoxiclav	0.03	0.016 – 8	96.8
Azithromycin	1	0.016 - >256	86.9
Cefaclor	1	0.25 - >256	-
Ceftriazone	0.25	0.016 – 4	93.4
Cefuroxime	0.25	0.016 – 16	92.5
Penicillin	0.06	0.016 - 8	89.1

*According to the following MIC breakpoints recommended by the National Committee for Clinical Laboratory Standards (NCCLS): co-amoxiclav, ≤0.5/0.25 mg/L; azithromycin, ≤0.5 mg/L; ceftriazone, ≤0.5 mg/L; cefuroxime, ≤0.5 mg/L; and penicillin, ≤0.06 mg/L

Table VIII: Antibiotic options in the case of penicillin-resistant *Streptococcus pneumoniae*

Site of treatment	Penicillin susceptibility	Antibiotic option
Out-patient	Penicillin-susceptible strains (MIC <2 µg/mL)	Oral amoxicillin, cefuroxime, cefprozil, macrolide, or antipneumococcal fluoroquinolone (moxifloxacin, gatifloxacin or levofloxacin)
General ward		Intravenous benzylpenicillin 2 mega units 4 hourly,[75] ampicillin 1 g 6 hourly, or ceftriaxone 1 g once daily
ICU	Penicillin-resistant strains (MIC ≥2 µg/mL)	Vancomycin, antipneumococcal fluoroquinolone or linezolid (high dose amoxicillin 3 g/day should be effective for strains with MIC 2-4 µg/mL)[76]

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MCQs on Community Acquired Pneumonia - A Malaysian Perspective

1. The following statements on the microbial aetiology of community acquired pneumonia are true:

a. In 'real world' practice the aetiological microorganism is identified in more than 50% of cases.
b. *Streptococcus pneumoniae* is the most commonly identified causative organism.
c. *Mycoplasma pneumoniae* is more frequently identified in younger patients without comorbitiy.
d. *Burkholderia pseudomallei* should be considered a possible causative organism in rural Southeast Asia particularly if the patient has diabetes mellitus.
e. There is a low incidence of *Legionella pneumonia* in studies conducted in Asian countries.

2. The following statements on community acquired pneumonia are true:

a. Infection due to *Mycobacterium tuberculosis* may present as community acquired pneumonia in Malaysia.
b. Culture of expectorated sputum is a reliable test for identification of the causative organism.
c. Recent findings show that less than 5% of *Haemophilus influenzae* isolates in Malaysia are β-lactamase producing.
d. Blood cultures are positive in 40% or more of cases.
e. Some *Streptococcus pneumoniae* strains are resistant to penicillins through the production of β-lactamase.

3. The following findings in patients with pneumonia indicate that the stated organism is definitely the aetiological agent:

a. Blood culture positive for *Streptococcus pneumoniae.*
b. Presence of *Legionella pneumophila* serogroup 1 antigen in the urine.
c. Sputum culture yields moderate growth of *Haemophilus influenzae.*
d. A fourfold rise in IgM antibody titre to *Mycoplasma pneumoniae.*
e. Isolation of *Pseudomonas aeruginosa* from pleural fluid collected from chest drain.

4. The following statements on the treatment of community acquired pneumonia are true:

a. The newer fluoroquinolones are effective against *Streptococcus pneumoniae.*
b. Antipseudomonal third generation cephalosporins are the antibiotic of choice in the treatment of most cases of community acquired pneumonia.
c. The antibiotic of choice in the empirical treatment of *Mycoplasma pneumonia* is a fluoroquinolone.
d. Pneumonia due to aspiration of oropharyngeal contents can be effectively treated with penicillin.
e. Metronidazole provides excellent coverage for Gram-positive anaerobes.

5. The following statements on the outcome of community acquired pneumonia treatment are true:

a. Antibiotic therapy that covers for both *Streptococcus pneumoniae* and atypical pathogens in hospitalised patients results in more favourable outcomes.
b. Mortality is higher in elderly patients.
c. High-level penicillin resistance is associated with increased mortality in *Streptococcus pneumoniae* pneumonia
d. Failure to identify a pathogen in patients with severe CAP has been associated with a worse outcome than if a pathogen is identified.
e. The implementation of treatment guidelines has been shown to reduce mortality and health care costs.