

# Community acquired pneumonia (cap) management



Community Acquired Pneumonia (CAP) is a form of acute lower respiratory tract infection that occurs in every 5 to 11 cases per 1000 adults' population every year. Amongst these cases, approximately 22% to 42 % of them are admitted to the hospital and of these percentages; about 1. 29 cases per 1000 person are of those in the age range of 18 to 39 years and about 13. 21 cases per 1000 person are above 55 years. The mortality of those admitted due to this disease in the UK falls within a variation of 5. 7% to 14%.

However, if CAP in adults is properly managed in the community, the number of deaths is considerably low at less than 1%. There are 2 types of CAP; one being the community acquired ones (which is most common) and hospital acquired ones (where by the CAP develops after 48 hours of admission). 1

CAP can be caused by a wide range of microorganisms. In the bacterial group, *Streptococcus pneumoniae* (Gram positive) is most common, especially winter, followed by *Haemophilus influenzae* (Gram negative), which are frequent in elderly patients. These 3 microorganisms are classified under the typical bacterial infection for CAP. The atypical pathogens include *Legionella pneumophila* (Gram negative), *Chlamydia sp.* (Gram negative) and *Mycoplasma pneumoniae* (Gram negative), which is harder to diagnose at early stages and are not sensitive to  $\beta$ -lactams. Other pathogens include viruses and fungi, which are not common in CAP. 1, 2

These pathogens enter the lower respiratory tract via these three routes: through the bloodstream from an infection not in the pulmonary site, aspiration of oropharyngeal contents, and inhaling it as aerosolized particle. 3 Bacteria is usually eradicated before it reaches the lungs, however as it invades the lungs, the bacteria enter the spaces between the cells and

between the alveoli through the connecting pores. This triggers the immune system to send neutrophils to the lungs to engulf and kill the bacteria as well as releasing cytokines leading to general activation of immune system, which leads to fever and fatigue. The neutrophils, bacteria, and fluid from the surrounding blood vessels would fill the alveoli, hence interrupting the normal oxygen transport. Some of the symptoms include cough, dyspnoea, fever ( $\approx 38^{\circ}\text{C}$ ), purulent sputum and pleuritic pain. 3

CAP is usually diagnose with sputum culture, testing with Gram staining and sensitivity to antibiotics. This however requires at least 24 hours to obtain the results, which consumes time. Chest X-ray, compared to sputum culture is faster, which makes it a good indicator. An oxygen saturation test would show a range of 94 to 98%, and in severe cases of pneumonia,  $\text{sPO}_2$  will be  $<92\%$ . Blood test should be carried out testing for full blood count (FBC), urinary and excretion (U & E), liver function test (LFT), C-reactive protein (CRP) and blood cultures. Pleural fluid can be aspirated to be cultured. 2, 3, 4

To assess the severity of the CAP, the 6 point score CURB-65 score can be used. One point is gain from each of the following assessment; Confusion, Urea  $> 7 \text{ mmol/l}$ , Respiratory rate  $> 30/\text{min}$ , low systolic ( $<90 \text{ mm Hg}$ ) or diastolic ( $\approx 60 \text{ mm Hg}$ ) Blood pressure, age  $> 65$  years. At CURB-65 score 0, the patient's condition is mild, having low risk of death and can consider outpatient management. At score 2, it is a moderate condition, whereby there is an increase risk of death, therefore inpatient management is required. At a score  $\approx 3$ , there is a high risk of death hence a severe case. This requires an urgent hospital admission. Different severity of CAP requires different treatment regimen. 1, 5

The primary treatment for CAP is antibiotics (Abx). One of the most common classes of Abx used is the  $\beta$ -lactams, which are penicillin and cephalosporin.  $\beta$ -lactams inhibit transpeptidase, an enzyme required for cross-linking peptide chains attached at the backbone of the peptidoglycan, which is required for cell wall synthesis of the bacterial. However, there are bacteria that produce  $\beta$ -lactamase, which deforms the structure of some  $\beta$ -lactams, therefore  $\beta$ -lactamase inhibitors such as clavulanic acid and tazobactam are used in conjunction with  $\beta$ -lactams. Macrolides work by binding to the 50s subunit of the bacterial ribosome, hence preventing translocation which in turn inhibits protein synthesis. Tetracyclines are another class of Abx that works on competing with tRNA at the binding site in the ribosome, therefore preventing translation hence protein synthesis. Next would be the fluoroquinolones. This class of Abx inhibits DNA gyrase or DNA topoisomerase II, which is needed to unwind the supercoils of DNA needed for replication and introduces negative supercoils. Another drug which is less commonly used is co-trimoxazole. This drug comprises of sulphamethoxazole and trimethoprim. Sulphamethoxazole is a sulphonamide; it competes for dihydropteroate synthetase with PABA (para-aminobenzoic acid) to produce folate and trimethoprim competes with folate for dihydrofolate reductase to produce tetrahydrofolate, whereby both these drugs lead to the inhibition of DNA production. 6

Evidence for treatment of the condition(s)

As mentioned above, treatment of CAP is based on the severity of the condition as well as the pathogen involved. Upon admission, patients should first be generally managed with oxygen therapy if needed, especially for

those whose arterial oxygen pressure ( $\text{PaO}_2$ )  $< 8 \text{ kPa}$  and/or  $\text{sPO}_2 < 94\%$ . The aim to this therapy is to maintain  $\text{PaO}_2 \geq 8 \text{ kPa}$  and  $\text{sPO}_2$  at about 94% to 98%. In hypercapnic ( $\text{PaCO}_2 > 6 \text{ kPa}$ ) respiratory failure COPD patients, controlled oxygen therapy should be given, beginning from 24% to 28%, to prevent rapid reduction of hypoxic drive. The aim for this is to maintain the  $\text{sPO}_2$  at about 88% to 92%, without having the pH blood level to fall below 7.35. Besides that, to those patients who lack the ability to move around should be started on unfractionated heparin or low molecular weight heparin (daltaparin) for prophylaxis of venous thromboembolism (VTE). 1

A study was carried out to prove an association of respiratory infection with increase risk of VTE. From a primary care general practice database, cases of first time diagnosed deep vein thrombosis (DVT) and pulmonary embolism (PE) who were above 18 years of age were selected. From these data, 4.0% of DVT cases with respiratory infection were found (0.6% in the earlier month) compared to a 2.3% in the control (0.2% in the earlier month), hence showing an increase risk of DVT in the month with an odds ratio of 2.64. There was also an increase risk of PE with an adjusted ratio of 2.50. Therefore, this showed that respiratory infection is indeed strongly associated with VTE. 7

Determination of empirical Abx choice upon admission is by the CURB-65 scaling the severity of the patient's condition. In mild cases, the preferred choice is Amoxicillin (a penicillin) 500mg tds (three times daily) taken orally if it is home treated. If the patient is to be treated in the hospital, IV (intravenous) Amoxicillin 500mg may be administered if the patient could not tolerate orally. The next choice in line is Doxycycline with a loading dose

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of 200mg, followed by 100mg, both taken orally or Clarithromycin 500mg bd (twice daily) taken orally as well. 1

In moderate cases, Amoxicillin 500mg to 1g tds and Clarithromycin 500mg bd both given orally is recommended as first line treatment. However, if the patient is not able to tolerate orally, there is a choice between Amoxicillin 500mg tds IV, or benzylpenicillin 1.2g qds (four time daily) IV together with Clarithromycin 500mg bd IV. The second line include either Doxycycline with a loading dose of 200mg, followed by 100mg, or levofloxacin 500mg od (once daily), or moxifloxacin 400mg od all taken orally. Moxicfloxcacin has been reported to have increase risk of adverse hepatic reaction, hence should be considered when initial treatment of infection is not suited to be used. 1

High severity cases require Abx to be given without delay. First line would be Co-amoxiclav 1.2g tds IV together with clarithromycin 500mg bd IV and if there is a strong suspicion on legionella, levofloxacin should be considered. There are 2 alternatives to this regimen; benzylpenicillin 1.2g qds IV adding either levofloxacin 500mg bd IV or ciprofloxacin 400mg bd IV, or Ceftriaxone 2g od IV or Cefuroxime 1.5g tds IV or Cefotaxime 1g tds IV together with clarithromycin 500mg bd IV and if there is a strong suspicion on legionella, levofloxacin should be considered as well. Macrolides are contraindicated with quinolones in increasing the risk of QT prolongation, which leads to ventricular arrhythmias, hence should not be used together. 1

Besides basing the treatment on severity, there are also pathogen specific treatments. The most common pathogen would be Streptococcus

pneumoniae. The treatment preferred includes Amoxicillin 500mg to 1g tds given orally or Benzylpenicillin 1. 2g qds IV. As a substitute to this choice, Clarithromycin 500mg bd is given orally, or Cefotaxime 1-2g tds IV or Ceftriaxone 2g od IV or Cefuroxime 0. 75 to 1. 5g tds IV. Next in line would be Haemophilus influenzae, a Gram negative bacterium. The preferred treatment would be Amoxicillin 500mg tds taken orally or administered IV. If the bacterium is one that produces  $\beta$ -lactamase, Co-amoxiclav 625mg tds given orally or 1. 2g tds on IV is chosen instead. On the second line to these drugs are either ceftriaxone 2 g od on IV or Cefuroxime 750 mg -1. 5 g tds on IV or cefotaxime 1-2 g tds on IV or fluoroquinolone (ciprofloxacin, levofloxacin or ofloxacin) on either orally or IV. 1

Amoxicillin is penicillin that has great activity on certain Gram positive and Gram negative bacteria, hence making it quite a broad spectrum Abx. However, in cases where the patient is found to be hypersensitive to penicillin, the alternative therapy is chosen, where it is usually either a macrolide or tetracycline. 1 Moreover, as mentioned above, this drug is susceptible to  $\beta$ -lactamase; therefore it is given together with clavulanic acid there are cases of bacteria producing  $\beta$ -lactamase. Co-amoxiclav is a combination of amoxicillin and clavulanic acid. A review done shown clinical studies done on respiratory tract infection produced a clinical rate response from 62% to 100% for those patients with CAP. 8 Co-amoxiclav is known to be associated with Clostridium Difficile Infection, affecting the bowel, especially the colon. However, co-amoxiclav is considered less likely to encourage overgrowth of C. diff in comparison to fluoroquinolones and cephalosporins. Moreover, the ability for switching IV to oral therapy without switching class

of agent (this encourages and early switch to oral therapy) will help in limiting C diff infection. 1

As seen in the case, Azithromycin is prescribed together with Co-Amoxiclav. A study was carried out in America, investigating a hospital claim-made database evaluating on the influence of initial Abx therapy to 30 day mortality, the hospital length of stay (LOS) and the total hospital costs. The Abx therapy consists of 5 different classes of Abx given in either by itself as a monotherapy or a dual therapy with an addition of a macrolide. In general, the mortality rate, LOS and total hospital charges significantly decline on patient who acquired the dual therapy as compared to those acquired the monotherapy. 9

Azithromycin is a macrolide, which has a longer half life, whereby it is a once daily dosage therapy with a short 3 day course therapy and allows a shorter duration of stay in the hospital. A study was done comparing Azithromycin with a 3 day course and Clarithromycin in a 10 day course. Both these drugs are used together with Ceftriaxone for the treatment of CAP. The severity score showed no significant difference between the two. Anyway, Azithromycin treated patients had a shorter duration of hospital admission compared to Clarithromycin, which in turn may result in a better compliance due to the shorter period of therapy. 10

Another study conducted on 501 subjects comparing a single 2.0g dose of Azithromycin and a 7 days therapy 1.0g extended-release formulation of Clarithromycin on safety and efficacy of mild-moderate CAP. Azithromycin had a 92.6% cure rate and 9.8% pathogen eradication rate as compared to



94. 7% on cure rate for extended-release Clarithromycin and 90. 5% on pathogen eradication rate. The therapeutic related side effects were at 26. 3% for Azithromycin and 24. 6% for extended-release Clarithromycin. Thus, this shows that a single 2. 0g dose of Azithromycin and the 7 days therapy 1. 0g extended-release formulation of Clarithromycin was almost as effective comparing each other in the treatment of mild-moderate CAP. 11

## Conclusion

This case involves in the use of Co-amoxiclav and Azithromycin in the management of CAP. Based on the evidences shown above, amoxicillin is preferred as the first line therapy. However, in the presence of the bacterium that produces  $\beta$ -lactamase enzyme, amoxicillin will be inactive, hence the need for clavulanic acid, where when used together with Amoxicillin forms Co-amoxiclav. Co-amoxiclav has shown great activity against resistant strains to  $\beta$ -lactam. However, this case has yet to have a sputum culture and sensitivity test done, hence should not be skipping steps in guidelines. Therefore, the use of amoxicillin at 500mg tds should suffice. Azithromycin in this case is used as a dual therapy with Co-amoxiclav. Based on the studies shown above, Azithromycin has proven to reduce mortality and reduce the stay in hospital as it is only a 3 day therapy, which in turns reduces the hospital costs. Besides that, having a once daily dosing is convenient, in which improves patient compliance. In conclusion, the treatment regimen recommended would be Amoxicillin 500mg tds for 7 days and Azithromycin 500mg OD for 3 days. If the sputum culture shows resistance to Amoxicillin, Co-amoxiclav 625mg tds should be recommended instead.