Empirical Antibiotics Study on Pneumonia in Intensive Care Unit

Yeni Farida, Katarina Puspita and Zahra Yusvida
Department of Pharmacy, Faculty of Mathematics and Science, Universitas Sebelas Maret, Ir.Sutami Street No. 36A Kentingan, Surakarta, Central Java, Indonesia

Keywords: Bacterial culture, Empiric antibiotics, Intensive care unit, Pneumonia

Abstract: Microorganisms and inflammatory cells are present in the air sacs of the lungs in most pneumonia patients, preventing their lungs from functioning normally. The main treatment for pneumonia is antibiotics supported by physiotherapy. This study aimed to determine the pattern of empirical antibiotic use and bacterial etiology (sputum culture test) of ICU patients at a government hospital in Madiun, West Java. This descriptive research used retrospective data collected from January to December 2016. The samples were purposively selected based on specific inclusion criteria (i.e., patients diagnosed with pneumonia who received antibiotic therapy and had information on their bacterial culture data). The study examined the medical records of 77 subjects who were mostly aged 0-5 years old (67.5%). *Acinetobacter baumannii* was the most commonly isolated organism (42.1%), followed by *Klebsiella pneumonia* and *Pseudomonas aeruginosa* (15.79%). Meropenem was mostly used as a single antibiotic in pediatrics (24%), while ceftriaxone was most common in adult (16.22%). The most widely used combinations of antibiotics were ampicillin and gentamycin for pediatrics ICU patient (20%) and meropenem and metronidazole for adult patients (13.51%). *Acinetobacter baumannii* was completely resistant to Ampicillin-sulbactam and partially resistant to other beta-lactam antibiotics. Both *Pseudomonas aeruginosa* and *Klebsiella pneumonia* were completely resistant to Ampicillin and Ampicillin-sulbactam.

1 INTRODUCTION

Pneumonia is one of the common infections that require hospitalization and is considered one of the top causes of death, especially in developing countries. Basic health research in Indonesia claims that pneumonia is the second leading cause of death after diarrhea (Indonesian Health Ministry, 2013). The mortality rate of hospitalized pneumonia patient is 15.5-24.8 % (Firmansyah *et al.*, 2015). Furthermore, the mortality rate for intensive care unit (ICU) patients with pneumonia remains high, approximately 15-50 % (Li *et al.*, 2016). Ventilator-associated pneumonia (VAP) is the most frequent infection in patients admitted to ICU (Chawla, 2008). Most deaths in pneumonia are attributable to VAP.

Empiric antibiotic therapy is highly recommended to begin soon after the diagnosis, which is within 6 hours, to reduce the mortality and morbidity rate (Harris *et al.*, 2017). Ideally, antibiotic therapy can cure pneumonia patients without causing complications or contributing to the development of antibiotic resistance (Stralin, 2008). IT requires proper antibiotic choice based on sputum bacterial sensitivity culture test. The bacterial etiology pattern of pneumonia differs from one region to another. The selection of antibiotics has to be based on the profile of the local bacterial etiology and antibiotic susceptibility (Hsueh *et al.,* 2011).

In this study, we determined the pattern of empirical antibiotic use and bacterial etiology based on sputum culture test.

2 MATERIALS AND METHOD

2.1 Study Design

The retrospective study was designed by collecting data from patients' medical record. The data included patient characteristics, empirical antibiotics use, bacterial culture information, and antibiotics susceptibility test data.

Farida, Y., Puspita, K. and Yusvida, Z.
Empirical Antibiotics Study on Pneumonia in Intensive Care Unit.
DOI: 10.5220/0008239200480053
In *Proceedings of the 1st Muhammadiyah International Conference on Health and Pharmaceutical Development (MICH-PhD 2018)*, pages 48-53
ISBN: 978-989-758-349-0

2.2 Patient and Setting

This study focused on ICU patients at a government hospital in Madiun, West Java starting from January until December 2016. Patients admitted to ICU during this period, who recieved antibiotic therapy for at least three days, and had bacterial culture data were eligible as samples in this study.

2.3 Data Analysis

The patient profile was analyzed descriptively by calculating the percentage of sex, age, length of stay (LOS), and the type of antibiotics use. The antibiotics use was grouped into two, namely single-use and combination. The percentage of each type of antibiotics use was calculated. Bacterial etiology and the pattern of antibiotics resistance were identified from the bacterial culture data.

3 RESULTS AND DISCUSSION

3.1 Patient Characteristic

This study involved 77 patients, including neonates, infants, toddlers, adults, and geriatrics. The age range of the patients was from 1 day old to 72 years old. No patients from the age range of child and adolescent were identified in this study. The distribution of patient age and gender is presented in Table 1.

The highest frequency of pneumonia cases was found in the age range of <5 years old. Other studies state that the incidence of pneumonia is dominant in population aged younger than 5 years old and older than 65 years old (Eida *et al.*, 2015; Rozenbaum *et al.*, 2015). However, in this study, the proportion of geriatric patients admitted to ICU is relatively small. The results of this study are in line with a study in the Philipines, a neighboring country of Indonesia, which claims that the majority of pneumonia episodes occurs in children aged < 2 years old (Kosai *et al.*, 2015).

Table 1: The characteristics of the patients observed in this study

Patient (N= 77)	Age	Gender		(%)
		Male	Female	
Neonates	0 – 1 month (n=17)	7	10	22.08
Infants	1 month – 2years (n=33)	17	16	42.96
Todlers	2–5 years (n=2)	2	-	2.60
Adults	18–64 years (n=18)	12	13	32.57
Geriatrics	≥ 65 years (n=7)	4	3	9.09

Table 1 also shows that the incidence of pneumonia is similar in male and female patients. In adult or geriatric patients, the incidence of pneumonia in both sexes is nearly similar. While many studies believe that gender contributed contributes to the risk factor of pneumonia differently (Falagas *et al.,* 2007; Rozenbaum *et al.,* 2015), another study reveals that mortality rate among pneumonia patients doesn not differ in gender (Gannon *et al.,* 2004). On the contrary, this study affirmed that either male or female had the same chance of contracting pneumonia. Nevertheless, compared with the other studies, this research had a limited number of samples.

There are any risk factors related to pneumonia. Besides age and sex, the other factors that contribute to the incidence of pneumonia are chronic comorbidities, exposure to cigarette smoke, alcohol abuse, malnutrition, conditions that promote pulmonary aspiration or inhibit coughing, and exposure to contaminated respiratory equipment. Unfortunately, this study could not evaluate these factors due to the lack of retrospective data.

The length of stay of the patients in the ICU ranged from 1 to 26 days. shows that most of the patients are hospitalized in the ICU for 0-7 days. The average lenght of stay is 8.5 days in pediatric patients and 9.5 days in adult and geriatric patients. It is substantially shorter than the result of a study in the Netherlands (i.e., 15.2 days) (Rozenbaum *et al.,* 2015).

3.2 The Bacterial Etiology and Antibiotic Susceptibility Test

The obstacles in this study lie in the limited bacterial culture data due to financial problem. Bacterial culture was not performed in all patients (19 out of 77 patients). Gram-negative bacteria were the dominant pathogen that caused pneumonia in this study. Gram-positive usually cause community-acquired pneumonia (CAP), while gram-negative bacteria are behind

Table 2: The length of stay in the intensive care unit (ICU)

Length of Stay (days)	Frequency (N=77)			Total
	Pediatric	Adult	Geriatric	
0 – 7	29	4	4	37
8 – 14	16	8	3	27
15 – 21	4	3	-	7
≥ 21	3	3	-	6

Table 3: The bacterial etiology in ICU

Bacterial type	Bacterial species	freq.	%
Gram-negative (N = 17)	*Acinetobacter baumannii*	8	42.11
	Klebsiella pneumonia	3	15.79
	Pseudomonas aeruginosa	3	15.79
	Pasteurella pneumotropic	1	5.26
	Pseudomonas oryzibabitans	1	5.26
	Stenotrophomonas maltophilia	1	5.26
Gram-positive (N = 2)	*Staphylococcus aureus (MRSA)*	1	5.26
	Staphylococcus aureus	1	5.26

hospital-acquired pneumonia (HAP) (Cukic and Hadzic, 2016). Based on the microbiological observation results, the most bacterial etiologic agents in ICU patients were *Acinetobacter baumannii* (42.11%), followed by *Klebsiella pneumonia* and *Pseudomonas aeruginosa* (15.79%). This result is in line with a study in Thailand and India (Chawla, 2008). A study in the United States also confirms that *Pseudomonas aeruginosa* and *Klebsiella pneumonia* are two of the three major microorganisms that cause HAP. The etiological bacteria in the observed patients are listed in Table 3.

Acinetobacter baumannii has high survivability and can form colonies outside the human body (Uwingabiye, 2017). It is discovered as the main nosocomial pathogen, that causes severe infections in patients treated in (ICUs) (Sileem *et al.*, 2017). A study in Poland reveals that *Acinetobacter baumannii* is the most frequent pathogen of VAP (53.3%) (Duszynska *et al.*, 2018).

Based on Figure 1, the isolated bacteria in ICU patients are resistanr to nearly all beta-lactam antibiotics. This study found that *Acinetobacter baumannii* was completely resistant to Ampicillin-sulbactam and partially resistant to other beta-lactam antibiotics. Both *Pseudomonas aeruginosa* and *Klebsiella pneumonia* were completely resistant to Ampicillin and Ampicillin-sulbactam. However, several cephalosporine antibiotics were not effective for treating the infections caused by *Pseudomonas aeruginosa* and *Klebsiella pneumonia*.

Aside from being resistance to beta-lactam antibiotics, the pathogens had developed the ability to adapt to Cotrimoxazole and Ciprofloxacin, except for *Acinetobacter baumannii*. Because *Pseudomonas aeruginosa* and *Klebsiella pneumonia* are highly resistant to gentamycin, this antibiotic is not preferable for treating their infections.

Multiple drug-resistant pathogens have increased in hospitalized pneumonia, especially in the ICU (Cilloniz *et al.*, 2016). The bacteria that causes HAP are more difficult to overcome due to its high resistance level to several antibiotics.

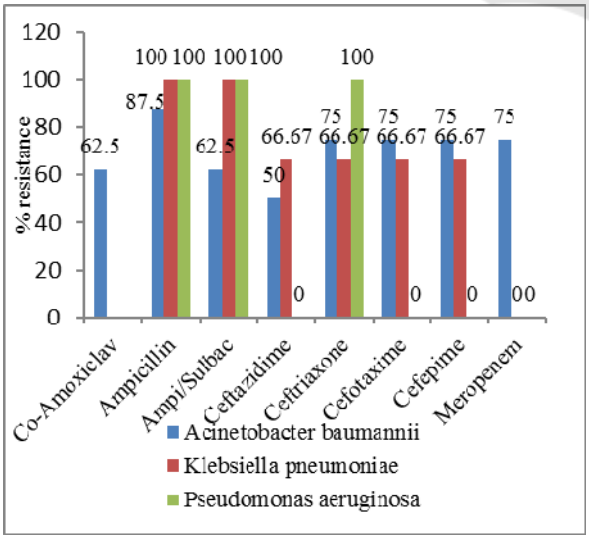

Figure 1: The pattern of bacterial resistance to beta-lactam antibiotics

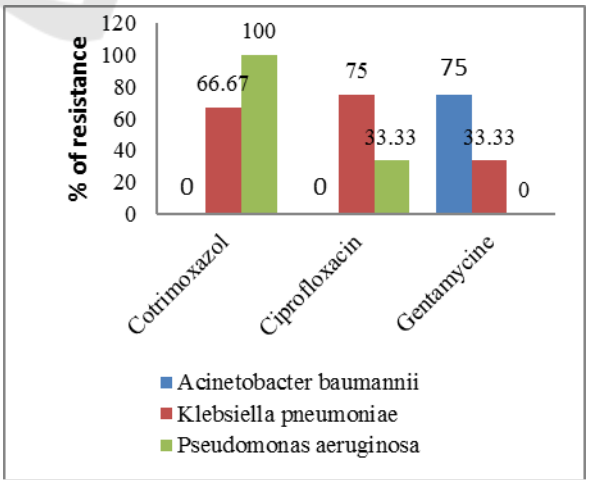

Figure 2: The pattern of bacterial resistance to other antibiotics

3.3 Empirical Antibiotics Use

Antibiotics are the major therapy in infection cases like pneumonia. The selection of appropriate antibiotics can increase the success rate of therapy and reduce the risk of death. A quick and precise administration of empirical antibiotics can immediately fix common symptoms of pneumonia, such as fever and rapid breathing or tachypnea (Hazir *et al.*, 2013).

The antibiotic use of the patients in this study presented in Tables 4 and 5. The mostly used single antibiotics in pediatric case are cefotaxime, while ceftriaxone is commonly prescribed to adult and geriatric patients. Cefotaxime is the most preferred antibiotics because of it is as effective as ampicillin-sulbactam to treat pneumonia (Puspitasari *et al*., 2014). Cefotaxim and ceftriaxone, the third generation of cephalosporine, are a broad-spectrum antibiotic. Patients with severe pneumonia should be treated with broad-spectrum antibiotics before the etiologic bacterial agent is detected (Stralin, 2008). Nevertheless, a study confirms that there are no differences in patient outcomes between the narrow-spectrum and the broad-spectrum antibiotic treatment (Williams *et al.*, 2013).

Based on Tables 4 and 5, Ampicillin-gentamycin is dominantly used in pediatric cases. In line with this study, (Lodha *et.al*., 2013) suggest the combination of ampicillin-gentamycin for pediatric inpatient with severe and very severe pneumonia. When combined with ampicillin, gentamycin produces a potent bactericidal effect. It increases the drug uptake by the inhibition of bacterial cell wall synthesis. Penicillin alters the structure of the cell wall, allowing gentamycin to penetrate easier into the bacteria (Katzung, 2014).

Meropenem is an empirical antibiotic for severe infection both in adult and pediatric patients (Baldwin *et al.,* 2008). Based on Table 5, the combination of meropenem and metronidazole is the most prescribed antibiotics in adult and geriatric patients. It is expected to achieve broader therapeutic targets and optimum ffects. Because these drugs work through the mechanism of inhibiting protozoan DNA synthesis, it

Table 4: The empirical antibiotic use in pediatric patients

Types of antibiotic use	Antibiotics	Number of use (N=47)	%	
Single	Cefotaxime	10	21.28	70.21
	Meropenem	7	14.90	
	Gentamycin	5	10.64	
	Ceftazidime	3	6.38	
	Metronidazole	2	4.26	
	Cefixime	2	4.26	
	Cefazoline	1	2.13	
	Ceftriaxone	1	2.13	
	Amikacin	1	2.13	
	Ampicillin	1	2.13	
Combina-tion	Ampicillin + Gentamycin	5	10.64	29.79
	Meropenem + Gentamycin	3	6.38	
	Meropenem + Amikacin + Metronidazole	1	2.13	
	Meropenem + Ampicillin	1	2.13	

Table 5: The empirical antibiotics use in adult and geriatric patients

Types of antibiotic use	Antibiotics	Number of use (N=42)	(%)	
Single	Ceftriaxone	9	21.43	69.05
	Meropenem	5	11.90	
	Cefotaxime	4	9.52	
	Ceftazidime	3	7.14	
	Gentamycin	2	4.76	
	Cefixime	2	4.76	
	Cotrimoxazole	1	2.38	
	Clindamycin	1	2.38	
	Cefadroxil	1	2.38	
	Ampicillin/ Sulbactam	1	2.38	
Combination	Meropenem + Metronidazole	3	7.14	30.95
	Ceftriaxone + Metronidazole	2	4.76	
	Gentamycin + Ceftriaxone	1	2.38	
	Gentamycin + Meropenem	1	2.38	
	Cefotaxime + Gentamycin	1	2.38	
	Clindamycin + Levofloxacin	1	2.38	
	Meropenem + Metronidazole	1	2.38	
	Ceftriaxone + Levofloxacin	1	2.38	
	Cefixime + Metronidazole	1	2.38	
	Meropenem + Metronidazole + Gentamycin	1	2.38	

results in cell death (Fauziyah *et al.*, 2011). Meropenem is more effective than cefotaxime for *P.aeruginosa* and isolated anaerobes. It is effective to treat nosocomial infections (Mehtar *et al.*, 1997). In this study, a patient infected with *Pseudomonas aeroginosa* and *Acinetobacter baumannii* recieved meropenem as an empirical antibiotic.

The selection of antibiotics according to the bacterial etiology can optimize the therapeutic effects and reduce the risk of resistance. Unfortunately, this study could not analyze the suitability of the empirical antibiotic to deal with certain isolated bacteria because the bacterial culture was not performed to all patients.

4 CONCLUSIONS

In this study, *Acinetobacter baumannii* was the most common isolated organism (42,11%), followed by *Klebsiella pneumonia* and *Pseudomonas aeruginosa* (15.79%). Meropenem was the most used single antibiotic in pediatric cases (24%), while ceftriaxone was most commonly prescribed adult patients (16.22%). The most widely used combination of antibiotics was ampicillin and gentamycin for pediatric ICU patients (20%), and meropenem and metronidazole in adult patients (13.51%). This study also found that *Acinetobacter baumannii* was completely resistant to Ampicillin-sulbactam and partially resistant to the other beta-lactam antibiotics. Both *Pseudomonas aeruginosa* and *Klebsiella pneumonia* were completely resistant to Ampicillin and Ampicillin-sulbactam.

ACKNOWLEDGMENTS

The authors would like to thank the Fundamental Grant, Universitas Sebelas Maret in 2018 for their financial assiatance.

REFERENCES

Baldwin, C. M., Lyseng-williamson, K. A. and Keam, S. J. (2008) 'Meropenem A Review of its Use in the Treatment of Serious Bacterial Infections', Adis Drug Evaluation, pp. 803–838.

Chawla, R. (2008) 'Epidemiology, etiology, and diagnosis of hospital-acquired pneumonia and ventilator-associated pneumonia in Asian countries', *American Journal of Infection Control*, 36(4 SUPPL.). doi: 10.1016/j.ajic.2007.05.011.

Cilloniz, C., Martin-Loeches, Garcia-Vidal C., San Jose A and Torres A. (2016) 'Microbial etiology of pneumonia: Epidemiology, diagnosis and resistance patterns', *International Journal of Molecular Sciences*, 17(12). doi: 10.3390/ijms17122120.

Cukic, V. and Hadzic, A. (2016) 'The Most Common Detected Bacteria in Sputum of Patients with Community-Acquired Pneumonia (CAP) Treated In Hospital', *Medical Archives*, 70(5), p. 354. doi: 10.5455/medarh.2016.70.354-358.

Duszynska, W. Litwin, A. Rojek, S. Szczesny, A. Ciasullo, A. Gozdzik, W.(2018) 'Analysis of Acinetobacter baumannii hospital infections in patients treated at the intensive care unit of the University Hospital, Wroclaw, Poland: A 6-year, single-center, retrospective study', *Infection and Drug Resistance*, 11, pp. 629–635. doi: 10.2147/IDR.S162232.

Eida, M.N, El-Maraghy M., Azab N., Khaled (2015) 'Pattern of hospital-acquired pneumonia in Intensive Care Unit of Suez Canal University Hospital', Egyptian Journal of Chest Diseases and Tuberculosis. *The Egyptian Society of Chest Diseases and Tuberculosis*, 64(3), pp. 625–631. doi: 10.1016/j.ejcdt.2015.03.028.

Falagas, M. E., Mourtzoukou, E. G. and Vardakas, K. Z. (2007) 'Sex differences in the incidence and severity of respiratory tract infections', Respiratory Medicine. *Elsevier*, 101(9), pp. 1845–1863. doi: 10.1016/j.rmed.2007.04.011.

Fauziyah, S. Radji, M. Nurgani, A (2011) 'Hubungan penggunaan antibiotika pada terapi empiris dengan kepekaan bakteri di icu rsup fatmawati jakarta'. Jurnal Farmasi Indonesia, 5(3), pp. 150–158.

Firmansyah, M A., Amin, Z., Loho, T. dan Shatri, H. 2015. Predictors of Mortality in Comunity-Acquired Pneumonia Inpatient in Cipto Mangunkusumo Hospital, Jakarta. *International Journal of CHEST Critical and Emergency Medicine*, 2 : 45-53.

Gannon T., J. McCaran K, Christopher J. Pasquale, Michaelter, Robert J. Napolitano, Lena M. (2004) 'Male gender is associated with increased risk for postinjury pneumonia.', Shock (Augusta, Ga.), pp. 410–414. doi: 10.1097/00024382-200405000-00003.

Harris, A.M, Bramley, A.M., Jain,S., Arnold, S.R., Ampofo, K., Self, W.H., *et.al*., (2017). 'Influence of Antibiotics on the Detection of Bacteria by Culture-Based and Culture-Independent Diagnostic Tests in Patients Hospitalized With Community-Acquired Pneumonia', Infectious Disease Society of America: Open Forum Infectious Disease, 30329: pp. 1-7.

Hazir T, Begum K, El Arifeen S, Khan AM, Huque MH, Kazmi N, Roy S, Abbasi S, Rahman QS, Theodoratou E, Khorshed MS, Rahman KM, Bari S, Kaiser MM, Saha SK, Ahmed AS, Rudan I, Bryce J, Qazi SA, Campbell H. (2013) 'Measuring coverage in MNCH: a prospective validation study in Pakistan and Bangladesh on measuring correct treatment of childhood pneumonia.', *PLoS medicine*, 10(5). doi: 10.1371/journal.pmed.1001422.

Hsueh PR, Hoban DJ, Carmeli Y, Chen SY, Desikan S, Alejandria M, *et al.*, . 2011 Consensus review of the

epidemiology and appropriate antimicrobial therapy of complicated urinary tract infections in Asia-Pacific region, *J Infect;*63(2):114-23

Indonesian Health Ministry. Indonesian Health Profile 2013. Indones Basic Res. 2014;1–100

Katzung, B. G., Masters, S. B. dan Trevor, A. J., (2014). Basic and Clinical Pharmacology,12th Edition, 900-1010, Mc Graw Hill Medical, New York.

Kosai, H. Tamaki, R. Saito, M. Tohma, K. Alday, P.P Tan, A.G. Inobaya, M.T Suzuki, A. Kamigaki, T. Lupisan, S.Tallo, V. Oshitani, Hitoshi (2015) 'Incidence and risk factors of childhood pneumonia-like episodes in Biliran Island, Philippines - A community-based study', *PLoS ONE*, 10(5), pp. 1–19. doi: 10.1371/journal.pone.0125009.

Li, Guowei Cook, Deborah J. Thabane, Lehana Friedrich, Jan O. Crozier, Tim M. Muscedere, John Granton, John Mehta, Sangeeta Reynolds, Steven C. Lopes, Renato D. Francois, Lauzier Freitag, Andreas P. Levine, Mitchell A.H. (2016) 'Risk factors for mortality in patients admitted to intensive care units with pneumonia', Respiratory Research. Respiratory Research, 17(1), pp. 1–9. doi: 10.1186/s12931-016-0397-5.

Lodha R, Kabra SK, Pandey RM. Antibiotics for community-acquired pneumonia in children. Cochrane Database Syst Rev [Internet]. 2013 Jun 4 [cited 2018 Sep 29];(6)

Mehtar, S. Dewar, E.P. Leaper, D.J. Taylor, E.W. (1997) 'A multi-centre study to compare meropenem and cefotaxime and metronidazole in the treatment of hospitalized patients with serious infections', *Journal of Antimicrobial Chemotherapy*, 39(5), pp. 631–638. doi: 10.1093/jac/39.5.631.

Puspitasari, D., Hasmono, D. and Rahman, T. (2014) 'Ampicillin Sulbactam and Cefotaxime Are Similarly Effective in Pediatric Pneumonia', pp. 116–121.

Rozenbaum, M. H. Mangen, Marie Josee J. Huijts, Susanne M. van der Werf, Tjip S. Postma, Maarten J. (2015) 'Incidence, direct costs and duration of hospitalization of patients hospitalized with community-acquired pneumonia: A nationwide retrospective claims database analysis', Vaccine. Elsevier Ltd, 33(28), pp. 3193–3199. doi: 10.1016/j.vaccine.2015.05.001.

Sileem, A. E., Said, A. M. and Meleha, M. S. (2017) '*Acinetobacter baumannii* in ICU patients: A prospective study highlighting their incidence, antibiotic sensitivity pattern and impact on ICU stay and mortality', *Egyptian Journal of Chest Diseases and Tuberculosis*. The Egyptian Society of Chest Diseases and Tuberculosis, 66(4), pp. 693–698. doi: 10.1016/j.ejcdt.2017.01.003.

Stralin, K. (2008) 'Usefulness of aetiological tests for guiding antibiotic therapy in community-acquired pneumonia.', *International journal of antimicrobial agents*. The Netherlands, 31(1), pp. 3–11. doi: 10.1016/j.ijantimicag.2007.06.037.

Uwingabiye, J. Frikh, M., Lemnouer, A. Bssaibis, F., Belefquih B., Maleb,A., Dahraoui S., Belyamani L., Bait A., Haimeur C., Louzi L., Ibrahimi, Elouennass, M.(2017) 'Intensive care unit-acquired *Acinetobacter baumannii* infections in a Moroccan teaching hospital: epidemiology, risk factors and outcome', Germs, 7(4), pp. 193–205. doi: 10.18683/germs.2017.1126.

Williams, D. J. Hall, M. Shah, S. S. Parikh, K. Tyler, A. Neuman, M. I. Hersh, A. L. Brogan, T. V. Blaschke, A. J. Grijalva, C. G.. (2013) 'Narrow Vs. Broad-spectrum Antimicrobial Therapy for Children Hospitalized With Pneumonia', *Pediatrics*, 132(5), pp. e1141–e1148. doi: 10.1542/peds.2013-1614.