Original Article

J Nepal Health Res Counc 2020 Oct-Dec;18(49): 661-6

DOI: https://doi.org/10.33314/jnhrc.v18i4.2566

Antimicrobial Susceptibility Pattern of Gram-Negative Bacteria Causing Lower Respiratory Tract Infections in Kathmandu University Hospital

Jatan B. Sherchan,[1] Sanjay Humagain[2]

[1]Department of Microbiology, Kathmandu University School of Medical Sciences, Dhulikhel, Nepal, [2]Department of Internal Medicine, Dhulikhel Hospital, Dhulikhel, Nepal.

ABSTRACT

Background: Respiratory tract infection due to Gram-negative bacteria is a common cause of morbidity and mortality worldwide. This study was carried out to determine the antimicrobial susceptibility pattern of Gram-negative bacteria from patients with lower respiratory tract infection visiting Kathmandu University Hospital.

Methods: A total of 3,403 respiratory samples including sputum and endotracheal aspirates were processed and antibiotic resistance pattern was determined following Clinical Laboratory Standard Institute guidelines. Patients' information was obtained after informed consent.

Results: Growth of Gram-negative bacteria was 210 (6.17%). 83(39.52%) were *Klebsiella pneumoniae* followed by *Escherichia coli, Pseudomonas aeruginosa*, *Acinetobacter species*, *Klebsiella oxytoca*, *Enterobacter species*, *Proteus mirabilis* and *Haemophilus influenzae*. 151(71.90%) isolates were multidrug resistant. None of the strains were resistant to colistin. 51(24.29%) were resistant to carbapenem and out of these 3(1.43%) were metallo-β lactamase producers. 89(65.92%) of the patients having both pneumonia along with other respiratory illnesses were above 60 years of age indicating that old age might be a predisposing factor. (p value is less than 0.0001). 92(81.42%) of patients of age above 60 years had multidrug resistant isolates indicating that old age might be a predisposing factor for getting infection my multidrug resistant isolates. (p value equals 0.0012) Among 36 diabetic patients 33(91.67%) had multidrug resistant isolates. Whereas out of 174 non-diabetic patients only 118(67.82%) had multidrug resistant isolates (p value equals 0.0037).

Conclusions: Multidrug-resistant Gram negative bacteria were observed in respiratory samples. Effective treatment of lower respiratory tract infection need detailed microbiological diagnosis and drug susceptibility testing.

Keywords: ESBL; LRTI; MBL; MDR

INTRODUCTION

Lower respiratory infections are the most deadly communicable disease, causing 3 million deaths worldwide in 2016.[1] In Nepal there were a total of 8,76,041 cases of lower respiratory tract infection in the year 2074/75.[2] Previous study in Nepal showed that among Gram-negative bacteria; *Klebsiella* spp., *Escherichia coli*, Pseudomonas spp., *Haemophilus influenzae*, *Acinetobacter* spp., commonly caused lower respiratory tract infection.[3]

Importance of ESBL-mediated infections has been increasingly recognized and resistance to other antibiotics has been noted among ESBL-producing *E. coli* and Klebsiella species.[4] This has led to the increased use of carbapenems but empirical treatment of suspected ESBL-producer infections with carbapenems has been associated with increase in carbapenem resistance.[5] The outcome of community acquired pneumonia has significant impact in elderly and diabetic patients.[6, 7]

This study aims to find out Gram-negative bacteria causing LRTI and their antibiotic resistance pattern along with few predisposing factors.

METHODS

The study was descriptive cross-sectional study, which was conducted at Microbiology lab of Kathmandu

Correspondence: Dr Jatan Bahadur Sherchan, Department of Microbiology, Kathmandu University School of Medical Sciences, Dhulikhel, Nepal. Email:jatansherchan @gmail.com, Phone: +9779808117533.

University Hospital, Dhulikhel from the month of November 2018 to October 2019. Ethical clearance was taken from Institutional Review Committee of Kathmandu University Hospital before the study was conducted. (Protocol approval number: 129/18)

All samples such as sputum, tracheal aspirate, endotracheal secretion and bronchial washings received from lower respiratory tract were included in the study and was processed for culture and sensitivity as recommended by Clinical Laboratory Standards Institute (CLSI) 2018.[8]

Patients with pulmonary Tuberculosis, atypical pneumonia and growth of normal flora were excluded from this study. After obtaining informed consent clinical data collection was done by history taking and clinical examination by the researcher himself with the help of consultant doctor taking care of the patient as well as by going through the medical and lab records.

The samples were cultured on Chocolate agar (CHA), 5% Sheep Blood agar (BA) and MacConkey agar (MA) plates. The CHA plates were incubated in CO_2 incubator (10% CO_2) at 37ºC for 24 hours while BA and MA plates were incubated at 37ºC for 24 hours in aerobic atmosphere. All the bacteria were isolated and identified using colony morphology, microscopy and biochemical tests following standard procedures.[8]

All the respiratory isolates were tested for antibiotic susceptibility by modified Kirby Bauer disc diffusion method in compliance with Clinical Laboratory Standards Institute (CLSI) 2018 guidelines on Mueller Hinton agar plates.[8] For Colistin susceptibility broth microdilution (BMD) method was done according to CLSI 2018 guidelines.[8]

Definition of ESBL: They are capable of hydrolyzing penicillins, broad-spectrum cephalosporins and monobactams, but they do not affect the cephamycins or carbapenems and their activity is inhibited by clavulanic acid.[9]

The initial screen test for the production of ESBL was performed by using ceftriaxone (CRO) (30 µg), ceftazidime (CAZ) (30 µg) and cefotaxime (CTX) (30 µg) disks (Oxoid, UK). If the zone of inhibition (ZOI) was ≤ 25 mm for CRO, ≤ 22 mm for CAZ and/or ≤ 27 mm for CTX, the isolate was considered a potential ESBL- producer as recommended by CLSI.[8]

Combination disk (CD) method was used for the phenotypic confirmation of ESBL-producing strains in which CTX and CAZ (30 µg), alone and in combination with clavulanic acid (CA) (10 µg) was used (Becton Dickinson, USA). An increased ZOI of ≥ 5 mm for either antimicrobial agent tested in combination with CA versus its zone when tested alone confirmed ESBL.[8]

Tests for MBL-production in Gram-negative isolates was done by Combination disk (CD) method in which two IPM disks (10 µg), one containing 10 µl of 0.1 M (292 µg) anhydrous Ethylene diamine-tetraacetic acid (EDTA) (Sigma Chemicals, St. Louis, MO), were placed 25 mm apart (center to center). An increase in zone diameter of >4mm around the IPM-EDTA disk compared to that of the IPM disk alone was considered positive for an MBL.[10]

Data were analyzed by (SPSS) version 11.5 software and P value less than 0.05 was considered significant.

RESULTS

Total number of sputum & other samples (tracheal aspirate, Endotracheal tube secretion etc.) received during the study was 3,403. Out of this growth of Gram-negative bacteria was only 210 (6.17%). This isolation rate would have increased if we had included Gram-positive bacteria also. 83(39.52%) of the isolates were *Klebsiella pneumoniae* followed by 59(28.09%) *Escherichia coli*, 40 (19.05%) *Pseudomonas aeruginosa*, 18(8.57%) Acinetobacter species, 6(2.86%) *Klebsiella oxytoca*, 2(0.95%) Enterobacter species, 1(0.48%) *Proteus mirabilis* and 1(0.48%) *Haemophilus influenzae*. Out of 210 isolates 151(71.90%) isolates were multidrug resistant.

Majority of *K. pneumoniae* strains, 70(84.34%) were resistant to Cefotaxime, Ceftriaxone and Amoxycillin-clavulanic acid, 69(83.13%) were resistant to Cefixime and Piperacillin-tazobactum, 68(81.93%) strains were resistant to Levofloxacin, Cefepime and Cefoparazone salbactum. 67(80.72%) strains were resistant to Ciprofloxacin, 66(79.52%) strains resistant to Cotrimoxazole and Gentamicin. Only 28(33.73%) strains were resistant to Amikacin and carbapenem group of drugs and none of the strains were resistant to Colistin as shown in table 1.

36 strains of *K. pneumoniae* were ESBL producer, 25 strains were sensitive only to Colistin by both disk diffusion as well as broth microdilution method and 11 strains were sensitive to all drugs.

Majority of *E. coli* strains, 53(89.83%) were resistant to Amoxycillin-clavulanic acid, Ciprofloxacin, Levofloxacin, Cefixime, Cefotaxime, Ceftriaxone, Cefepime and

Gentamicin. 51(86.44%) strains were resistant to Cotrimoxazole and Cefoperazone-salbactum. 49(83.05%) strains were resistant to Piperacillin-tazobactum. Only 22(37.29%) strains were resistant to Amikacin, only 6(10.17%) strains were resistant to Carbapenems and none of the strains were resistant to Colistin as shown in table 1.

31 strains of *E. coli* were ESBL producer, 6 strains were sensitive only to Colistin and 5 strains were sensitive to all drugs.

All *K. oxytoca* strains were resistant to Cotrimoxazole. 5(83.33%) were resistant to Amoxycillin-clavulanic acid, Ciprofloxacin, Levofloxacin, Cefixime, Cefotaxime, Ceftriaxone, Cefepime, Cefoperazone-salbactum, Piperacillin-tazobactum, Gentamicin. 1(16.67%) strains were resistant to Carbapenems. None of the strains were resistant to Amikacin and Colistin as shown in table 1.

Enterobacter strains were resistant to Amoxycillin-clavulanic acid and Cefotaxime. 1 (50%) strains were resistant to Cotrimoxazole, Ciprofloxacin, Levofloxacin, Cefixime, Ceftriaxone, Cefepime, Cefoperazone-salbactum, Piperacillin-tazobactum and Gentamicin. None of the strains were resistant to Amikacin, Carbapenems and Colistin as shown in table 1.

The only one strain of *P. mirabilis* was not resistant to any antibiotics.

Table 1. Antibiotic resistance pattern of *K. pneumoniae* and *E. coli*.

Antibiotics/ Organism	*K. pneumoniae (n=83)*	*E. coli (n=59)*	*K. oxytoca (n=6)*
Amoxycillin clavulanic acid	70(84.34%)	53(89.83%)	5(83.33%)
Cotrimoxazole	66(79.52%)	51(86.44%)	6(100%)
Ciprofloxacin	67(80.72%)	53(89.83%)	5(83.33%)
Levofloxacin	68(81.93%)	53(89.83%)	5(83.33%)
Cefixime	69(83.13%)	53(89.83%)	5(83.33%)
Cefotaxime	70(84.34%)	53(89.83%)	5(83.33%)
Ceftriaxone	70(84.34%)	53(89.83%)	5(83.33%)
Cefepime	68(81.93%)	53(89.83%)	5(83.33%)
Cefoperazone-salbactum	68(81.93%)	51(86.44%)	5(83.33%)
Piperacillin-Tazobactum	69(83.13%)	49(83.05%)	5(83.33%)
Gentamicin	66(79.52%)	53(89.83%)	5(83.33%)
Amikacin	28(33.73%)	22(37.29%)	0(0.00%)
Imipenem	28(33.73%)	6(10.17%)	1(16.67%)
Meropenem	28(33.73%)	6(10.17%)	1(16.67%)
Colistin	0(0.00%)	0(0.00%)	0(0.00%)

5(12.5%) of *P. aeruginosa* were resistant to Ciprofloxacin, Ceftazidime. 3(7.5%) were resistant to Levofloxacin, Cefepime, Gentamicin. 2(5%) were resistant to Piperacillin-tazobactum, Amikacin and Carbapenems. No strains were resistant to Colistin as shown in table 2.

17(94.44%) of Acinetobacter were resistant to Ciprofloxacin, Levofloxacin, Ceftazidime, Cefotaxime, Cefepime. 16(88.89%) were resistant to Piperacillin-tazobactum and Cefoperazone-salbactum. 14(77.78%) were resistant to Gentamicin and Carbapenems. 11(61.11%) were resistant to Amikacin. No strains were resistant to Colistin as shown in table 2.

Table 2. Antibiotic resistance pattern of *Pseudomonas aeruginosa* (n=40) and *Acinetobacter.*

Antibiotics/ Organism	*P. aeruginosa (n=40)*	*Acinetobacter (n=18)*
Ciprofloxacin	5 (12.50%)	17 (94.44%)
Levofloxacin	3 (7.50%)	17 (94.44%)
Ceftazidime	5 (12.50%)	17 (94.44%)
Cefotaxime		17 (94.44%)
Cefepime	3 (7.50%)	17 (94.44%)
Cefoperazone-salbactum		16 (88.89%)
Piperacillin-Tazobactum	2 (5.00%)	16 (88.89%)
Gentamicin	3 (7.50%)	14 (77.78%)
Amikacin	2 (5.00%)	11 (61.11%)
Imipenem	2 (5.00%)	14 (77.78%)
Meropenem	2 (5.00%)	14 (77.78%)
Colistin	0 (0.00%)	0 (0.00%)

Single strain of *H. influenzae* was not resistant to any antibiotics.

Out of total Gram negative isolates in the study 51(24.29%) were resistant to carbapenem and out of these 3(1.43%) were metallo-β lactamase (MBL) producers.

Regarding the clinical profile, 75(35.71%) patients had only pneumonia and no other respiratory illnesses whereas remaining 135(64.29%) had pneumonia with acute exacerbation of chronic obstructive pulmonary disease and other illnesses. Within this 89(65.92%) of the patients having both pneumonia along with other respiratory illnesses were above 60 years of age. Among patients having only pneumonia 25(33.33%) of the patients were above 60 years of age. This indicated that old age might be a predisposing factor for both illnesses together. (P value is less than 0.0001)

Among 113 patients who were above age 60 years,

92(81.42%) had MDR isolates and among 97 patients who were below age 60 years, only 59(60.82%) had MDR isolates. This indicated that again old age might be a predisposing factor for getting infection my MDR isolates. (P value equals 0.0012)

Among 36 diabetic patients 33(91.67%) had MDR isolates. Whereas out of 174 non-diabetic patients only 118(67.82%) had MDR isolates. (P value equals 0.0037)

DISCUSSION

The study detected Gram negative bacterial isolates from lower respiratory tract infection and found antibiotic resistance pattern. Few risk factors were also determined. Growth of Gram-negative bacteria out of total sample was only 6.17%, which is much less compared to the study conducted by Mishra et al, in which the growth of Gram negative bacteria isolate was 40%.[11] The reason why we observed so less isolates here might be because we did not include Gram positive isolates in our study.

Klebsiella pneumoniae is a prominent opportunistic pathogen for hospital-acquired and community-acquired infections such as pneumonia, urinary tract infection and pyogenic liver abscess.[12] Our study found that the most common isolate causing LRTI was *K. pneumoniae* 39.52%, followed by *E. coli*, *P. aeruginosa*, Acinetobacter species, *K. oxytoca*, Enterobacter species, *P. mirabilis* and *H. influenzae*. Other studies also observed that *K. pneumoniae* was the commonest gram negative isolate in lower respiratory tract infection.[13]

Problem of multidrug resistance seems to be more prominent in our setting since we observed that 71.90% isolates were multidrug resistant, and out of this 1.43% were metallo-ß lactamase (MBL) producers which are more than the finding of Mishra et al, in which 53.7% were MDR and 1.3% was MBL producers.[11]

Colistin was found to be the best drug for *K. pneumoniae*. But more than 79% were resistant to cephalosporins, penicillins and penicillin with beta-lactamase inhibitor, fluoroquinolones, cotrimoxazole and gentamicin. But only 33.73% strains were resistant to amikacin and carbapenems. 43.37% of *K. pneumoniae* were ESBL producer. In our study colistin seemed to be useful for the treatment of carbapenem resistant *K. pneumoniae* strains which has also been mentioned in article by Petrosillo et al.[14]

For *E. coli*, again colistin seemed to be the best drug. But more than 80% strains were resistant to cephalosporins, penicillins and penicillin with beta-lactamase inhibitor, fluoroquinolones, gentamicin and cotrimoxazole. Only 37.29% strains were resistant to amikacin and only 10.17% strains were resistant to carbapenems. ESBL production was more among *E. coli*, 52.54% in comparison to *K. pneumoniae*. Carbapenemase production seemed less among *E. coli* in comparison to *K. pneumoniae* which agrees with the findings by Jean et al.[15]

In our study in contrast to *K. pneumoniae*, for *K. oxytoca* beside colistin, amikacin also seemed to be best drug. But all strains were resistant to cotrimoxazole and more than 80% strains were resistant to cephalosporins, penicillins and penicillin with beta-lactamase inhibitor, fluoroquinolones and gentamicin. Only 16.67% strains were resistant to carbapenems. Carbapenemase producing *K. oxytoca* causing pneumonia has also become an issue recently and has been reported in other studies too.[16,17]

None of the Enterobacter strains were resistant to amikacin, carbapenems and colistin. But both strains were resistant to amoxycillin-clavulanic acid and 50% strains were resistant to cephalosporins, fluoroquinolones, cotrimoxazole, piperacillin-tazobactum and gentamicin. Multidrug resistant Enterobacter has also emerged as a causative agent of systemic infections in the past in other centers also.[18] The only one strain of *P. mirabilis* was not resistant to any antibiotics.

In case of *P. aeruginosa* again colistin seemed to be best drug. 5% were resistant to piperacillin-tazobactum, amikacin and carbapenems. Carbapenem resistance among *P. aeruginosa* isolates from lower respiratory tract infection in our study was much less than the findings of Gladstone et al, in which it was 42.8%.[19]

In case of Acinetobacter too none of the strains were resistant to colistin. 77.78% were resistant to gentamicin and carbapenems. Only 61.11% were resistant to amikacin. In our center carbapenem resistance among Acinetobacter was much more than the findings of Gladstone et al, in which it was only 14.2%.[19] Hence, it is necessary for our center to control antibiotic resistance among Acinetobacter. The only one strain of *H. influenzae* isolated in our study was not resistant to any antibiotics.

Out of total Gram negative isolates in the study 24.29% were resistant to carbapenem and out of these 1.43% were metallo-ß lactamase (MBL) producers which is much less than the finding of Mishra et al, in which it was 9.7%.[11]

65.92% of the patients having both pneumonia along with other respiratory illnesses were above 60 years of age. Among patients having only pneumonia 33.33% of the patients were above 60 years of age. This indicated that old age might be a predisposing factor for both illnesses together (p value is less than 0.0001).

COPD seemed to be the most frequent comorbid condition present in elderly patients with pneumonia. Similar findings has been found by Restrepo et al.[20]

81.42% of the patients of age above 60 years had MDR isolates and only 60.82% of the patients of age below 60 years had MDR isolates. This indicated that again advancing age might be a predisposing factor for getting infection my MDR isolates (p value equals 0.0012). Drug resistant bacterial pneumonia in elderly patients was also found in study conducted by Feng et al.[21]

In our study 91.67% of diabetic patients had MDR isolates. Whereas only 67.82% of non-diabetic patients had MDR isolates (p value equals 0.0037). This indicates that diabetes might be a risk factor for acquiring lower respiratory tract infection by MDR bacteria which might even lead to morbidity and mortality of the patients. Such type of finding has been mentioned in the study conducted by Kornum et al.[22]

Some of the limitations of this study might be the study duration was short and patients were much less to determine all possible bacteria causing lower respiratory tract infection. All possible risk factors were not determined. Molecular analysis of the isolates was not performed.

CONCLUSIONS

The present study showed that *Klebsiella pneumoniae* was the commonest Gram negative bacteria causing lower respiratory tract infection. Increasing multidrug resistance especially ESBL producers and carbapenem resistance along with predisposing factors such as diabetes and old age have become a major concern. Management of lower respiratory tract infection in the community as well as hospital by early investigation and analysis of infection and controlling of risk factors might help to reduce the burden of respiratory tract infection in healthcare centers and community.

ACKNOWLEDGEMENTS

We express our profound gratitude to Department of Microbiology and Department of Internal Medicine, Kathmandu University Hospital for their kind support and co-operation throughout this study.

REFERENCES

1. WHO | The top 10 causes of death. Available from: https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death.
2. Government of Nepal,Ministry of Health and Population,Department of Health Services Kathmandu. Annual Report 2074/75 (2017/18). Available from: https://dohs.gov.np/annual-report-2074-75/
3. Khan S, Priti S, Ankit S. Bacteria Etiological Agents Causing Lower Respiratory Tract Infections and Their Resistance Patterns. Iran Biomed J. 2015; 19 (4):240-6.[PubMed]
4. Nijssen S, Florijn A, Bonten MJM, Schmitz FJ, Verhoef J, Fluit AC. b-Lactam susceptibilities and prevalence of ESBL-producing isolates among more than 5000 European Enterobacteriaceae isolates. Int J Antimicrob Agents 2004; 24:585–91.[PubMed]
5. Wong-Beringer A. Therapeutic challenges associated with extendedspectrum, b-lactamase–producing Escherichia coli and Klebsiella pneumoniae. Pharmacotherapy 2001; 21:583–92.[PubMed]
6. Stupka JE, Mortensen EM, Anzueto A, Restrepo MI. Community-acquired pneumonia in elderly patients. Aging health 2009;5(6):763-774.[PMC]
7. Saibal MA, Rahman SH, Nishat L, Sikder NH, Begum SA, Islam MJ, et al. Community acquired pneumonia in diabetic and non-diabetic hospitalized patients: presentation, causative pathogens and outcome. Bangladesh Med Res Counc Bull. 2012 Dec;38(3):98-103.[PubMed]
8. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 28th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2018. https://clsi.org/media/1930/m100ed28_sample.pdf
9. Paterson DL, Bonomo RA. Extended-spectrum betalactamases: a clinical update. Clin Microbiol Rev.2005;18: 657- 86.[PubMed]
10. Franklin C, Liolios L, Peleg AY. Phenotypic detection of carbapenem-susceptible Metallo-beta-lactamase-producing Gram-negative bacilli in the clinical laboratory. J Clin Microbiol. 2006;44:3139-44.[PubMed]
11. Mishra SK, Acharya J, Kattel HP, Koirala J, Rijal BP, Pokhrel BM. Metallo-beta-lactamase producing gram-negative bacterial isolates. J Nepal Health Res Counc. 2012 Sep;10(22):208-13.[PubMed]
12. Spagnolo AM, Orlando P, Panatto D, Perdelli, F, Cristina

ML. An overview of carbapenem-resistant Klebsiella pneumoniae: epidemiology and control measures. Rev Med Microbiol 2014;25:7–14. [Article]

13. Nepal R, Shrestha B, Joshi DM, Joshi RD, Shrestha S, Singh A. Antibiotic Susceptibility Pattern of Gram-negative Isolates of Lower Respiratory Tract Infection. J Nepal Health Res Counc 2018 Jan-Mar;16(38):22-6.[PubMed]

14. Petrosillo N, Giannella M, Lewis R, Viale P. Treatment of carbapenem-resistant Klebsiella pneumoniae: the state of the art. Expert Rev Anti Infect Ther. 2013 Feb;11(2):159-77.[PubMed]

15. Jean SS, Lee NY, Tang HJ, Lu MC, Ko WC, Hsueh PR. Carbapenem-Resistant Enterobacteriaceae Infections: Taiwan Aspects. Front Microbiol. 2018;9:2888.[PubMed]

16. Hoenigl M, Valentin T, Zarfel G, Wuerstl B, Leitner E, Salzer HJF et al. Nosocomial outbreak of Klebsiella pneumoniae carbapenemase-producing Klebsiella oxytoca in Austria. Antimicrob Agents Chemother. 2012;56(4):2158–2161. [PMC]

17. Labrador I, Araque M. First Description of KPC-2-Producing Klebsiella oxytoca Isolated from a Pediatric Patient with Nosocomial Pneumonia in Venezuela. Case Rep Infect Dis. 2014;2014:434987.[Link]

18. Grazziotin AL, Vidal NM, Palmeiro JK, Dalla-Costa LM, Venancio TM. Genome Sequencing of Four Multidrug-Resistant Enterobacter aerogenes Isolates from Hospitalized Patients in Brazil. Front Microbiol. 2016;7:1649.[FullText]

19. Gladstone P, Rajendran P, Brahmadathan KN. Incidence of carbapenem resistant nonfermenting gram negative bacilli from patients with respiratory infections in the intensive care units. Indian J Med Microbiol. 2005 Jul;23(3):189-191.[Article]

20. Restrepo MI, Sibila O, Anzueto A. Pneumonia in Patients with Chronic Obstructive Pulmonary Disease. Tuberc Respir Dis (Seoul). 2018;81(3):187–197.[PubMed]

21. Feng H, Yan S, Chen Y, Zhu C, Wang L. Risk factors of drug-resistant bacterial pneumonia in elderly inpatients in Shandong Province. Biomedical Research 2017; 28 (13): 5780-5784. [Article]

22. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. Diabetes Care. 2007 Sep;30(9):2251-7.[Article]