Review

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MODERN ASPECTS OF COMMUNITY-ACQUIRED PNEUMONIA IN PATIENTS WITH DIABETES MELLITUS

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Clinical importance of the community-acquired pneumonia clinical course and treatment in patients with diabetes mellitus is discussed in this review. Clinical characteristics, immunological parameters, possible drugs regimen, depending on community-acquired pneumonia severity, and the ability to optimize therapy with antibacterial drugs are considered. The features of the appointment of antibacterial drugs in the step-down antibacterial therapy, peculiarities of pneumonia in patients with diabetes mellitus.

KEY WORDS: diabetes mellitus, pneumonia, outcomes, antibacterial treatment

СУЧАСНІ АСПЕКТИ НЕГОСПІТАЛЬНОЇ ПНЕВМОНІЇ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ

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Клінічну значимість перебігу негоспітальної пневмонії та її лікування у пацієнтів із цукровим діабетом було обговорено у даному огляді. Клінічні характеристики, імунологічні показники, можливі режими антибактеріальних препаратів, в залежності від тяжкості течії негоспітальної пневмонії, а також можливість оптимізації терапії антибактеріальними препаратами були обговорені. Розглянуто особливості призначення антибактеріальних препаратів під час ступінчастої антибактеріальної терапії, особливості перебігу пневмонії у пацієнтів з цукровим діабетом.

КЛЮЧОВІ СЛОВА: цукровий діабет, пневмонія, результати, антибактеріальна терапія

СОВРЕМЕННЫЕ АСПЕКТЫ ВНУТРИБОЛЬНИЧНОЙ ПНЕВМОНИИ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ

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Клиническая значимость течения внебольничной пневмонии и ее лечения у пациентов с сахарным диабетом была обсуждена в данном обзоре. Клинические характеристики, иммунологические показатели, возможные режимы антибактериальных препаратов, в зависимости от тяжести течения внебольничной пневмонии, а также возможность оптимизации терапии антибактериальными препаратами были обсуждены. Рассмотрены особенности назначения антибактериальных препаратов при ступенчатой антибактериальной терапии, особенности течения пневмонии у пациентов с сахарным диабетом.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет, пневмония, исходы, антибактериальная терапия

INTRODUCTION

In the northern hemisphere the annual incidence of community-acquired pneumonia (CAP) is about 12 cases per 1,000 people, the biggest part of CAP cases occur during the wintertime [1]. Total number of adult patients with CAP in five biggest European countries (Britain, France, Italy, Germany, Spain) exceeds around 3 million people [2]. In Ukraine annual CAP morbidity is 3-11 cases per 1000 adults and the highest ranges usually observed among older patients [3]. CAP clinical course as one of the most common infectious diseases have certain characteristics associated with patient age, presence

concomitant diseases, drug interactions between medication for the basic treatment of concomitant diseases and antibacterial therapy of CAP, which can cause an additional risks and change the prognosis of patients [4–8]. Older age and concomitant diseases such as diabetes (DM), heart failure, chronic obstructive pulmonary disease, chronic renal failure, liver disease, immunodeficiency, increase the risk of CAP incidence and disease outcomes in that case will be worse [9]. Since 2006, each year in the USA with a diagnosis diabetes mellitus are hospitalized around 6 million of patients. 8–12 % of them - because of various infectious diseases. Patients with diabetes in 2 times more often hospitalized because infectious diseases diagnosis than patients without it. Since 2006, about 10 million of diabetic patients were hospitalized in the ICU. Infectious diseases such as premium cause of hospitalization observed in 10 % of cases of annual diabetes mellitus patient's hospitalization [10].

IMMUNE SYSTEM CHANGES IN PATIENTS WITH DIABETES MELLITUS AS A CAUSE OF HIGH RISK OF INFECTIOUS DISORDERS

Increased susceptibility and increased mortality from CAP in patients with diabetes mellitus could be explained by specific changes in these patients' immunity and response to infections. The main pathophysiologic mechanisms which are responsible for altered immunity function are: increased virulence of some pathogens because of hyperglycemia; glycosuria, decreased production of interleukins during infection response; reducing of chemotaxis and phagocytic abilities, polymorph nuclear leukocytes immobilization; gastrointestinal and urinary dysmotility [11–14]. For example, decreased secretion of interleukin-1 and interleukin-6 by mononuclear cells and monocytes in response to stimulation by lipopolysaccharides [11, 15]. Hyperglycemia reported as the cause of decreased mobilization of polymorph nuclear leukocytes, chemotaxis, and phagocytic activity [16–18]. Also high level of glucose in DM patients lead to block of the inhibiting glucose-6-phosphate dehydrogenase (G6PD), increased apoptosis of polymorph nuclear leukocytes, and reducing their transmigration through the endothelium and as result of it - decreased leukocytes antimicrobial function [15]. Some studies reveal that the biological function of the antibodies becomes impaired with increasing of glycated hemoglobin levels [19]. Experimental animal models of inflammation and in humans confirm the compromised immune response in patients with diabetes: increased pro-inflammatory [20–21], and antyfibrinolitic pro-coagulating activity, increased expression of cell surface receptors, which can recognize foreign agents [22]. Cytokines may increase blood glucose levels by stimulating gluconeogenesis and increasing insulin resistance in peripheral tissues and in the liver [23-24]. In pneumonia patients with concomitant diabetes hyperglycemia were significantly higher compared with patients with diabetes alone (level of HbA1c 8, 2 % and 7, 2 % respectively, $p < 0.01$). Worse hyperglycemia control leads to the increased incidence of pneumococcal pneumonia in patients with diabetes, but high levels of hyperglycemia during hospitalization did not lead to increasing of disease severity [25]. For patients with diabetes, taking in account that more than two-thirds of them have two or more comorbidities [26], respiratory infections has long been considered as inflammation precipitators. In this situation the challenge is the complicity of the diagnosis making based only on clinical and radiological findings. But some of clinical studies showed absolutely opposite results. For example, The GenIMS Study confirmed that serum concentrations of biomarkers of inflammation (Tumor Necrosis Factor - α, interleukin – 6 and interleukin – 10), coagulation (antithrombin, factor IX) and fibrinolysis (PAI-1 and D-dimers) are similar among patients with diabetes and non-diabetes patients when measured during the first week of the treatment. In a large number of patients serum cytokine levels were within the normal range [27] and diabetes did not affect the concentration of other biomarkers [23, 28]. The degree of increased releasing of primary inflammation mediators is closely connected with the clinical variant of the disease [29].

ETIOLOGICAL CAUSES OF CAP IN PATIENTS WITH DM: STREPTOCOCCUS PNEUMONIAE? ACINETOBACTER? OR NOTHING SPECIAL?

In the case of patients with diabetes, in the global scientific medical literature there is no sufficient information regarding the clinical characteristics and microbiological factors of CAP [30]. In patients with diabetes, there are

two important microbiological points of view of the peculiarities of pneumonia. First is the increased importance of specific etiologic pathogens (S. aureus, gram-negative strains) in CAP development. Second is an identified susceptibility to more severe and complicated course of pneumonia, caused by S. pneumoniae, with frequent bacteremia appearance. Another distinction of respiratory infections in these patients is a frequent occurrence of bacterial superinfection and ketoacidosis during the influenza season [31]. Saibal M.A.A. et al. [32] compered in their study total 47 diabetic and 43 non-diabetic adult hospitalized patients with CAP and in 7 (20.0 %) cases more than one organism was isolated from sputum samples. Klebsiella pneumoniae was the most commonly isolated organism from sputum sample and its level was higher in the group of DM patients than in non-DM group (19,1 vs 4,7 % respectively). But Streptococcus pneumoniae incidence in sputum species were higher in the non-DM group (0,0 vs 20,7 % respectively). Also in the group of DM patients were found 2 (4,3 %) E. Coli, 2 (4,3 %) Pseudomonas aeruginosa and 1(2.9 %) Acinetobacter grows, that weren't present in sputum samples of non-DM patients. These findings were similar to the previous international investigations data, such significantly increased risk of Acinetobacter spp. as a possible causative agent of CAP in patients with concomitant diabetes in Ljubic S. et al. investigation made in Croatia. Infections caused by Acinetobacter spp. usually are difficult to treat because of its rapidly developed antibacterial resistance and more than 60 % mortality from pneumonia in this case [33–34]. The main pathogens that were the cause of CAP has developed in hospitalized patients with type 2, according to Russian researchers are S. pneumoniae (32,9 %), S. aureus (16,5 %), H. influenza (15,2 %), K. pneumoniae (13,9 %) and M. pneumoniae (12,7 %) [35]. Patients suffering from diabetes, often die from invasive pneumococcal pneumonia comparing to those without diabetes. Moreover, in patients with diabetes are often prevalent unfavorable prognostic factors of pneumococcal bacteremia such as advanced age and presence of comorbidities [36]. In patients with diabetes due to esophagus paresis episodes of esophageal contents micro aspiration from oropharynx or stomach are prevalent compering with non-DM patients. According to some authors [37–38], because of this phenomenon in diabetic patient's aspiration pneumonia most likely pathogens can be aerobic bacteria (S. pneumoniae, S. aureus and K. pneumoniae).

FEATURES OF CAP CLINICAL COURSE IN DM: WHY THESE PATIENTS ARE SO SPECIAL?

By the presence of all those factors written above could be explained more severe and complicated pneumonia clinical course reported in the global scientific medical literature. One of the latest investigations were made in Portugal 2016 year [39], as this country presents one of the highest rates of DM in Europe. Clinical cases of CAP with DM were compared with CAP without DM in age and gender subgroups, hospitalization time and mortality rate, across age groups and over the 2009–2012 periods. Compared to patients with CAP without DM (61.9 %) average length of stay in CAP with DM cases was significantly longer ($p < 0.0001$), with an average length of stay was 12.0 ± 10.5 vs 11.2 ± 10.1 days respectively. Also, in-hospital mortality (20–79 years), adjusted for sex and age, was significantly higher in patients with CAP who have DM as compared to patients with CAP without DM (15.2 % vs 13.5 %, $p = 0.002$). Interesting is the fact that, when cohort was analyzing by age group, increased mortality of patients with DM was only observed in the youngest age group. These findings can be explained by presence of the prevalence type 1 diabetes cases represented in the youngest age group (20–39 years; 26.8 %) with more severe DM clinical course, frequent pneumonia complication as pleurisy and presence of ketoacidosis episodes during the treatment period. In a meta-analysis, which included 33,148 patients with CAP, were demonstrated increased mortality among patients with diabetes (odds ratio 1.3; 95 % confidence interval (CI) 1,1–1,5) [40]. However, this study was based on high levels of glucose in patients without confirmed diagnosis of diabetes. However, modern clinical reports provide strong evidence of increased vulnerability to infections in diabetic patients, who are not only at increased risk for severe and current infections but rather infections are the most common cause of destabilization of diabetes and in 20–25 % of cases is the first DM manifestation [31]. For example, in a population cohort study that included 29.900

patients [41] was studied whether DM increases the risk of death and complications from pneumonia. According to the data, the adjusted risk of mortality at 30 and 90 days was 1.2 (95 % CI 1.1–1.3) and 1.10 (95 % CI 1,02–1,18) for patients with diabetes. But the difference between the groups of patients with diabetes and without regarding the number of episodes of pulmonary complications or bacteremia was not found. High levels of blood glucose during hospitalization was associated with an increase in deaths rate of patients (adjusted risk of 30-day mortality for high blood glucose levels equal to 1.46 (95 % CI 1,01–2,12)). It is important that after the reduction and normalization of blood glucose levels after admission to the hospital, diabetes was no longer associated with increased levels of mortality (risk of death in diabetic patients with blood glucose within 6,1–11,0 mmol/l was 0,96 (95 % CI 0,69–1,35)). Since hyperglycemia is an essential feature of diabetes, conceptually difficult to separate the impact of blood glucose levels from the effects of diabetes only. In a large study, which covered 623,718 patients aged ≥ 65 years with the level of mortality 10.6 %, was confirmed adverse relationship between total in-hospital mortality and diabetes (OD 1.27; 95 % CI 1,23-1,31) in patients with pneumonia [42-43]. According to the order № 128 of Ministry of Health of Ukraine from 19.03.2007, patients with pneumonia and concomitant DM referred to the group with risk factors of high deaths risk and adverse disease outcome [44]. Summarizing all written above could be named features of CAP in patients with DM. They are: Diabetes increases the risk of hospitalization of patients with CAP; Community-acquired episodes of pneumonia in patients with diabetes require a longer hospital stay; Diabetes affects mortality hospitalized patients with CAP (increases).

WHERE TO TREAT CAP PATIENTS WITH CONCOMITANT DM: AMBULATORY, HOSPITAL WARD OR ICU?

There are two important issues that are widely discussed in medical society in the context of CAP treatment: where and how to treat these patients? To determine the appropriate place of treatment and the range of appropriate diagnostic procedures is very important to determine the severity of the disease. According to the order № 128 of Ministry of Health of Ukraine from 19.03.2007 patients with pneumonia and concomitant DM as II clinical group of CAP (mild clinical CAP course in patients with concomitant diseases) could be treated or ambulatory either as III clinical group (CAP with moderate clinical course) can be hospitalized to the hospital due to clinical judgment of physician or inability to take medicine, receive appropriate care during pneumonia treatment. If patient with DM has severe CAP, this group of patients should be treated in ICU units [44]. How physician can define the clinical course severity of CAP in patients with DM? Leading international and national guidelines for CAP treatment [45–46] recommend basing the choice of antibacterial treatment and the place of CAP treatment on specific instruments that allow determining the severity of the disease when diagnosis was made. Such as prognostic model Pneumonia Severity Index (PSI) or scales CURB-65/CRB-65 (confusion, uremia, respiratory rate, low blood pressure, age 65 years or greater) [47–48] which usually supplemented with physician determination of subjective factors as the ability to safely and reliably take oral-parenteral medication and the availability of outpatient support resources [49–50]. Ambulatory patients who have a CRB-65 score of 0 are at low risk of death and do not normally require hospitalization for clinical reasons; patients who have a CRB-65 score of 1 or 2 are at increased risk of death, particularly with a score of 2, and hospital referral and assessment should be considered; patients who have a CRB-65 score of 3 or more are at high risk of death and require urgent hospital admission. If measurement of urea level could be provided, CURB-65 should be used for determination of CAP severity [44, 50–51]. In Hai-yan Li et al. (2016) study were found that CURB-65 score could be simplified by removing low blood pressure because CUR-65 score of ≥ 2 for prediction of mortality was better than that of a CURB-65 score of ≥ 3 and it might be a more valuable cutoff value for severe CAP [51]. PSI is most commonly used prognostic model in the world named also PORT (according to the study Pneumonia Patient Outcomes Research Team), in which provides the definition of 20 main pneumonia clinical parameters. Evaluation of these parameters as patients age, presence/absences of the main comorbidities, level of heart rate or blood pressure etc., allows determine pneumonia severity index data,

predict the risk of lethal outcome and provide recommendations for treatment and places of empirical CAP antibacterial treatment [44, 50–52]. Mazen S. Bader et al. (2016) in late research found that appearance of CAP complications in patients with DM were associated with the first antibiotic dose prescribed > 8 hours after hospitalization (odds ratio = 3.16; 95 % CI: 1.58–6.32; p = 0.001) and with index PORT scale (PSI) > 90 (odds ratio = 3.52; 95 % CI: 1.45–8.53; p = 0.005). An increasing the length of stay in hospital was associated with: the first antibiotic dose > 8 hours with hospitalization [HR] = 0.56, p = 0.01 and with index scale PORT (PSI) > 90 (HR = 0.62, p = 0.01), CAP symptoms duration before hospitalization (HR = 0.96, p = 0.04) and CAP pre-hospital antibacterial therapy (HR = 0.90, p ≤ 0.0001) [53, 54].

HOW TO TREAT CAP PATIENTS WITH CONCOMITANT DM: DOES ANY SPECIFIC RECOMMENDATION EXIST?

American College of Family Physicians not revealed any specific recommendations for the treatment of respiratory infections in patients with diabetes. In Europe, these patients are usually treated in outpatient medical departments. In Ukraine specific guidelines for treatment of CAP in patients with DM weren't created and this category of patients can be referred to II, III or IV clinical groups of patients depending of the severity of CAP [44]. International experts offer three strategies for duration of CAP treatment: 1) based on the current clinical course of CAP; 2) based on the etiological reason – treatment is continuing in accordance with specified pathogen; and 3) the duration of treatment is determined according to an antibacterial drug that has been selected for treatment [44, 49–50]. Before prescription an antibacterial treatment of CAP in patients with DM should be considered: interactions of antimicrobial drugs with glucose-lowering drugs; probable reduced medication absorption during intramuscular and oral drugs administration in patients with diabetes due to the development of diabetic microangiopathy; probability of serious complications such as ketoacidosis and multiple infections; careful control of blood glucose levels in a patient not depending of the cause of hospitalization. When the first dosage of antibacterial drug should be prescribed for diabetes patients with CAP? According to the latest guidelines all patients should receive antibacterial treatment since the diagnosis CAP was made, but not later than 4 hours after hospitalization in a medical institution. In case of severe CAP, first dosage of antibacterial drug can be assigned by a family doctor prior to hospitalization [50]. Prescription of the antibacterial therapy more than 4 hours from the time of diagnosis CAP was made increases the level of in-hospital mortality in patients with diabetes (OR 6.5, 95 % CI 2.2 – 18.8, p = 0.001) [53]. Summarizing guidelines for CAP treatment: for patients with mild (low) severity CAP should be prescribed oral monotherapy by amoxicillin or if its needed parenteral injections of amoxicillin or benzyl penicillin, or clarithromycin [53], in Ukraine preferable drugs are monotherapy with amoxicillin/sulbactam or cefuroxime or their combination with macrolides [44]. Patients with CAP moderate severity should be treated with monotherapy of amoxicillin or macrolide if patients have failed to respond to an adequate course of amoxicillin before admission. In case if parenteral rout of prescription is needed, combination of amoxicillin or benzyl penicillin, together with clarithromycin is preferable [53]. Ukrainian recommendations suggest using combinations of β-lactam (parenteral) with macrolide (per os) and respiratory fluoroquinolones as drugs of other choice [44]. Patients with CAP high severity should receive a parenteral combination of a broad-spectrum β-lactamase stable antibiotic together with a macrolide or a second-generation (e.g., cefuroxime) – third-generation (e.g., cefotaxime or ceftriaxone) cephalosporin can be used instead of broad-spectrum β-lactamase stable antibiotic, together with macrolide [53]. Ukrainian recommendations suggest prescribing of combinations of β-lactam (parenteral amoxicillin/clavulonate or cephalosporin's III generation) with macrolide and respiratory fluoroquinolones as drugs of another choice [44]. How long antibiotics should be given for CAP patients? In patients with moderate clinical course of CAP antibacterial treatment could be discontinued in 3–5 days after normal ranges of body temperature will be stabilizing. For those with high severity microbiologically - undefined pneumonia, 7–10 days of treatment is proposed. This length of treatment could be extended to 14 or 21 days according to clinical judgement of physician [44, 53]. When should the intravenous route be switched to oral? Step –

down antibacterial treatment provides a two – phase's antibiotics prescription: when parenteral route of drugs administration in early treatment phases could be switched to oral immediately after stabilization of the clinical state of the patient. The advantages of step - down therapy is the reducing of the duration of parenteral treatment, which provides a significant reduction in the cost of treatment and the patient's length of stay in hospital with maintaining high clinical efficiency [55–57]. In this type of drugs prescription preferred is the usage of antimicrobial drugs with two dosage forms – both for parenteral administration and for application per os. Selected drug must also has a high bioavailability, doesn't interact with other drugs, being are well tolerated, have a long half-life and provide optimal cost of treatment [56, 58]. Patients treated initially with parenteral antibiotics should be transferred to an oral regimen as soon as clinical improvement occurs and the temperature has been normal for 24 h, providing there is no contraindication to the oral route. The antibiotic choices for the switch from intravenous to oral are onward where there are effective and equivalent oral and parenteral formulations. For example in the case of initial parenteral cephalosporin's prescription, the oral switch could be made to amoxicillin/clavulonate 625 mg three times daily rather than to oral cephalosporin with low per oral bioavailability. Or if patient was initially treated with combination of benzyl penicillin + levofloxacin in case of severe CAP, after stabilization of the patients state this therapy could be switched to oral levofloxacin with or without oral amoxicillin 500 mg–1.0 g three times daily [53, 58].

CONCLUSION

Despite absence of specific guidelines for CAP treatment in patients with concomitant DM, this patients should be treated carefully because of: increased risk of infectious pathology, presence of the macro and micro complications of DM which can affect antibacterial drugs bioavailability and both diseases clinical course; pathological changes in immunity of DM patients with decreasing of immune reactivity to infectious agents; specific medication interactions between antibacterial drugs and glucose lowering agents as respiratory fluoroquinolones interactions with glucose lowering agents could lead to severe hypoglycemia; high risk of DM and CAP complication.

REFERENCES

1. Guidelines for the management of adult lower respiratory tract infections - Summary / Woodhead M., Blasi F., Ewig S. [et al.] // Clin. Microbiol. Infect. – 2011. – № 17 (6). – p. 1–24.
2. National Vital Statistics Reports Hyattsville, MD: National Center for Health Statistics [e- resurs] / Heron M. P., Hoyert D. L., Murphy S. L. [et al.] (2009) Deaths: Final data for 2006. – 2009. // Access link: http://www.cdc.gov/nchs/fastats/pneumonia.html
3. Kuznetsova L. F. Rational strategy of pharmacotherapy of patients with community-acquired pneumonia at elderly and senil eage / Kuznetsova L. F., Bogoslav T. V., Reshetilov Yu. I. // Zaporozhye medical journal. – 2014. – № 2. – p. 36–38
4. Kozlov R.S. Negospitalna pnevmoniya: Standarti diagnostiki, suchasna antibakterialna terapiya / Kozlov R.S., Pertseva T.S., Dmitrichenko V.V. [et al.] // Ukrainsky medichny chasopis. – 2011. – № 6 (85). – p. 59–63.
5. Diabetes mellitus and infection: an evaluation of hospital utilization and management costs in the United States / Elsevier. - March 2015 // Access link: doi: http://dx.doi.org/10.1016/j.jdiacomp.2014.11.005
6. Bereznyakov I. G. Antibacterial pneumonia in patients with community-acquired pneumonia in the hospital / Bereznyakov I. G. // Clinical Immunology. Allergology. Infectology. – 2008. – № 5. - p. 22–26.
7. Community-acquired pneumonia in adults. Practice Guidelines for diagnosis, treatment and prevention: a manual for physicians / [Chuchalin A. G., Sinopalnikov A. I., Kozlov R. S. [et al.]. – M., 2010. – 106 p.
8. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis / Fine M. J., Smith M. A., Carson C. A. [et al.] // JAMA. – 1996. – № 275. – p. 134–141.
9. Capelastegui A. Study of community-acquired pneumonia: incidence, patterns of care, and outcomes in primary and hospital care / Capelastegui A., Espaňa P.P., [et al.] // J. Infect. – 2010. – № 61. – p. 364–371.
10. The official website of the United Nations Organization / [electronic resource]. – Access link: http/www.un.org/russian.

11. Casqueiro J. Infections in patients with diabetes mellitus: A review of pathogenesis / Casqueiro J., Casqueiro J., Alves C. // Indian J Endocrinol Metab. – 2012 // Access link: doi: 10.4103/2230–8210.94253.
12. Endeman H. Systemic cytokine response in patients with community-acquired pneumonia / Endeman H., Meijvis S. C. A., Rijkers G. T. [et al.] // Eur. Respir. J. – 2011. – № 37. – p. 1431–1438.
13. Bereznyakov I.G. infections and antibiotics / Bereznyakov I.G. – Kh: Constant, 2004. – 447 p.
14. Stegenga M. E. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis / Stegenga M. E., Vincent J. L., Vail G. M. [et al.] // Crit. Care Med. – 2009. – № 38. – p. 539–545.
15. Peleg A.Y. Common infections in diabetes: Pathogenesis, management and relationship to glycaemic control / Peleg A. Y., Weerarathna T., McCarthy J. S., Davis T.M. // Diabetes Metab Res Rev. – 2007. – № 23:3 – p. 13.
16. Nirmal J. Infections in patients with diabetes mellitus. / Nirmal J, Caputo GM, Weitekamp MR, Karchmer AW. // N Engl J Med. – 1999. – № 341. – p. 1906–12.
17. Vardakas K. Z. Diabetes mellitus as a risk factor for nosocomial pneumonia and associated mortality / Vardakas K. Z., Siempos I. I., Falagas M. E. // Diabet Med. – 2007. – №24. – p. 1168–71.
18. Geerlings S. E. Cytokine secretion is impaired in women with diabetes mellitus / Geerlings S.E., Brouwer E.C., Van Kessel K. C., Gaastra W., Stolk R. P., Hoepelman A. I. // Eur J Clin Invest. – 2000. - №30. – p. 995–1001.
19. Cano M, Iglesias P, Pérez G, Díez JJ. Influenza A virus (H1N1) infection as a cause of severe diabetic ketoacidosis in type 1 diabetes. Endocrinol Nutr. – 2010. – №57. – p. 37–8.
20. Aliberti S. Incidence, etiology, timing, and risk factors for clinical failure in hospitalized patients with community-acquired pneumonia / Aliberti S., Amir A., Peyrani P. [et al.] // Chest. – 2008. – № 134 (5). – p. 955–962.
21. Krogh-Madsen R. Effect of hyperglycemia and hyperinsulinemia on the response of IL-6, TNF-{alpha}, and FFAs to low-dose endotoxemia in humans / Krogh-Madsen R., Moller K., Dela F. [et al.] // Am. J. Physiol. Endocrinol. Metab. – 2004. – № 286. – p. 766–772.
22. Stegenga M. E. Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia / Stegenga M. E., van der Crabben S. N., Blümer R. M. [et al.] // Blood. – 2008. – № 112. – p. 82–89.
23. Avdeev S.N. C-reactive protein - new or old marker bronchopulmonary infections? / Avdeev S.N., Baymakanova G.E. // Atmosphere. Pulmonology and Allergology. – 2008. – № 4. – p. 26–32.
24. Baker E. H. Hyperglycemia and pulmonary infection. / Baker E. H., Wood D. M., Brennan A. L. [et al.] // Proc. Nutr. Soc. – 2006. – № 65. – p. 227–235.
25. Yende S. The influence of pre-existing diabetes mellitus on the host immune response and outcome of pneumonia: analysis of two multicentre cohort studies / Yende S., van der Poll T., Lee M. J. [et al.] for the GenIMS and Health ABC study // Thorax. – 2010. – № 65. – p. 870–877.
26. Johnson E. L. Treatment of Diabetes in Long-Term Care Facilities: A Primary Care Approach / Johnson E. L., Brosseau J. D., Soule M., Kolberg J. // Clin. Diabetes. – 2008. – Vol. 26, № 4. – p. 152–156.
27. Niederman M. S. Recent advances in community-acquired pneumonia: inpatient and outpatient / Niederman M. S. // Chest. – 2007. – № 131. – p. 1205–1215.
28. Blasi F. Biomarkers in lower respiratory tract infections / Blasi F., Stolz D., Piffer F. // Pulmonary Pharmacology & Therapeutics. – 2010. – № 23. – p. 501–507.
29. Skopintsev M.A. Pathogenic aspects of the formation of a systemic inflammatory response in patients with community-acquired pneumonia: Abstract. Dis. for the degree of kand. med. nauk. Sciences: spec. 14.00.16 «Pathological physiology» / Skopintsev M. A. - Kemerovo, 2006. – 24 p.
30. Menendez R. Duration of length of stay in pneumonia: influence of clinical factors and hospital type / Menendez R., Cremades M. J., Martınez-Moragon E. [et al.] // Eur. Respir. J. – 2003. – № 22. – p. 643–648.
31. Bogun L. V. Infectious diseases in patients with diabetes mellitus / Bogun L. V. // Bolezni I antibiotiki. – 2009. – № 1 (1). – p. 24–29.
32. Saibal M. A. A. Community acquired pneumonia in diabetic and non-diabetic hospitalized patients: presentation, causative pathogens and outcome/ Saibal M. A. A., Rahman S. H. Z., Nishat L., Sikder N. H., Begum S. A., Islam M. J., Uddin K. N.// Bangladesh Med Res Counc Bull. – 2012. – № 38. – p. 98–103.
33. Ljubic S. Pulmonary infections in patients with diabetes / Ljubic S., Balachandran A., Pavlic-Renar I., Barada A., Metelko J. // Diabetologia Chroatica. – 2004. - № 33 (4). – p.115–124/

34. Edis E. C. Acinetobacter pneumonia: Is the outcome different from the pneumonias caused by other agents? / Edis E. C., Hatipoglu O. N., Tansel O., Sut N. // Annals of Thoracic Medicine. – 2010. – Vol.5 (2). – p. 92–96.
35. Schmidt N. V. The structure and antibiotic resistance of pathogens of community-acquired pneumonia in patients with diabetes mellitus type 2 // Clinical Microbiology and Antimicrobial Chemotherapy, abstracts of the XIV International Congress IACMAC / ESCMID for antimicrobial therapy. – 2012.
36. Thomsen R. W. Diabetes and Outcome of Community- Acquired Pneumococcal Bacteremia / Thomsen Reimar W., Johnsen Soren P. [et al.]. // Diabetes Care. – 2004. – № 27. – p. 70–76.
37. Ikegame S. A Retrospective Analysis of 111 Cases of Pneumococcal Pneumonia: Clinical Features and Prognostic Factors / Ikegame S., Wakamatsu K., Kumazoe1 H., Kawasaki M. // Intern Med. – 2012. – № 51. – p. 37–43.
38. Von Baum H. Community-acquired pneumonia through Enterobacteriaceae and Pseudomonas aeruginosa: diagnosis, incidence and predictors / von Baum H., Welte T., Marre R., Suttorp N., Ewig S.for the CAPNETZ study group // Eur Respir J. – 2010. – № 35. – p. 598–605.
39. Martins M. Diabetes hinders community-acquired pneumonia outcomes in hospitalized patients / Martins M., Boavida J. M., Raposo J. F., Froes F., Nunes B., Ribeiro R. T., Macedo M. P., Penha-Gonçalves C. // BMJ Open Diab Res Care. – 2016. // Access link: doi:10.1136/bmjdrc-2015-00018
40. Labarere J. Comparison of Outcomes for Low-Risk Outpatients and Inpatients With Pneumonia : A Propensity-Adjusted Analysis / Labarere J., Stone R. A., Obrosky D. S., Yealy D. M. [et al.] // Chest. – 2007. – № 131. – p.480–488.
41. Kornum J. B. Type 2 diabetes and pneumonia outcomes: a population-based cohort study / Kornum J. B., Thomsen R. W., Riis A., Lervang H. H., Schønheyder H. C., Sørensen H. T. // Diabetes Care. – 2007. – № 30. – p.2251–225.
42. Kaplan V. Hospitalized community-acquired pneumonia in the elderly: age – and sex-related patterns of care and outcome in the United States / Kaplan V., Angus D. C., Griffin M. F. [et al.] // Am J Respir Crit Care Med. – 2002. – № 165. – p. 766–772.
43. Stegenga M. E. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis / Stegenga M. E., Vincent J. L., Vail G. M. [et al.] // Crit Care Med. – 2009. – № 38. – p. 539–545.
44. Mandate №128 od 19.03.2007r. About zatverdzhennya klinichnih protokoliv nadannya medichnoï Relief for spetsialnistyu «Pulmonologiya» / Ministry of Health of Ukraine - Ofits. vidannya – Singapore – 2007, 146 p. – (Normative documents of Ministry of Health of Ukraine).
45. Endeman H. Clinical features predicting failure of pathogen identification in patients with community acquired pneumonia / Endeman H., Schelfhout V., Voorn G. P. // Scandinavian Journal of Infectious Diseases. – 2008. – № 40. – p. 715–720.
46. Ewig S. New perspectives on community-acquired pneumonia in 388,406 patients. Results from a nationwide mandatory performance measurement programme in health-care quality / Ewig S., Birkner N., Strauss R., Schaefer E., Pauletzki J., Bischoff H., [et al.]. // Thorax. – 2009. – № 64. – p. 1062–1069.
47. Stralin K. Definite, probable and possible bacterial aetiologies of community-acquired pneumonia at different CRB-65 scores / Stralin K., Olcen P., Tornqvist E., Holmberg H. // Scandinavian Journal of Infectious Diseases. – 2010. – № 42. – p. 426–434.
48. Lim W. S. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. / Lim W. S., Macfarlane J. T., Boswell T. C., [et al.] // Thorax. – 2001. – № 56 (4). – p. 296–301.
49. Vnebol'nichnaya pnevmoniya u vzroslykh: prakticheskiye rekomendatsii po diagnostike, lecheniyu i profilaktike / Posobiye dlya vrachey // Rossiyskoye respiratornoye obshchestvo. – Moskva, 2010 g. – S. 1–106.
50. Lim W. S. 2015 - Annotated BTS Guideline for the management of CAP in adults (2009) / Lim W. S., Smith D. L., Wise M. P., Welham S. A. on behalf of the British Thoracic Society // Thorax. – 2015 // Access link*:* doi:10.1136/thoraxjnl-2015 –206881
51. Hai-yan Li. CUR-65 Score for Community-Acquired Pneumonia Predicted Mortality Better Than CURB-65 Score in Low–Mortality Rate Settings / Hai-yan Li, Qi Guo, Wei-dong Song [et all.] // 2015. – Access link: http://dx.doi.org/10.1097/MAJ.0000000000000545
52. Heppner H.J. Pneumonia Severity Index (PSI), CURB-65, and mortality in hospitalized elderly patients with aspiration pneumonia / Heppner H. J., Sehlhoff B., Niklaus D., Pientka L., Thiem U. // Z Gerontol Geriatr. – 2011. – № 44 (4). – p. 229–34.
53. Mazen S. Bader. Community-Acquired Pneumonia in Patients With Diabetes Mellitus: Predictors of Complications and Length of Hospital Stay / Mazen S. Bader [et al.] // Amer.Jour.of Science. – 2016. – Vol. 352, Issue 1. – p. 30–35.

54. Johns Hopkins Antibiotic Guidelines 2015-2016. Treatment Recommendations For Adult Inpatients. 2015. – p.64 // Access link: http://www.hopkinsmedicine.org/amp/guidelines/antibiotic_guidelines.pdf
55. Simonov S. S. Sequential therapy of bacterial respiratory infections in the practice of the family doctor / Simonov S. S. // Ukr.med.zhurnal. – 2014. – № 5 (103) – p. 40–46.
56. Bereznyakov I. G. Step-down therapy in the treatment of bacterial infections. : Questions and Answers / Bereznyakov I. G. // News of medits. and pharmacy. – 2011. – № 11–12. – p. 371–372.
57. Yudina L. V. The choice of antibiotic therapy with a combination of acute infections of the upper and lower respiratory tract. / Yudina L. V. // Ukrain. medy. Chasopis – 2013. – № 6 (98). – p. 43–46
58. Negospitalna ta nozokomialna (gospitalna) pnevmoniya u doroslih osib: klinichni nastanovi, Ukraine // Health of Ukraine. – 2013. – № 18. – p. 35–37.