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Original Article

The expression and the clinical significance of eosinophils, PCT and CRP in patients with acute exacerbation of chronic obstructive pulmonary disease complicated with pulmonary infection

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Abstract: Objective: To investigate the expression and clinical significance of eosinophil (EOS), procalcitonin (PCT) and C-reactive protein (CRP) in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) complicated with pulmonary infection. Methods: All of the 167 AECOPD patients treated in our hospital were included as the research subjects for this retrospective study. The patients were divided into an infected group (n=41) and a non-infected group (n=126) according to the presence or absence of pulmonary infection. Etiological analysis and antimicrobial susceptibility test were performed on patients in the infection group, and the levels of serum PCT, CRP and EOS were compared between the two groups. According to the forced expiratory volume in one second (FEV1), the pulmonary function of the infection group was divided into 1-3 grades, and the levels of CRP, PCT and EOS in different grades were compared. The correlation between the levels of CRP, PCT, EOS and the ratio of FEV1/FVC (forced vital capacity) in infection group was analyzed. The ROC curve was used to analyze the clinical value of CRP, PCT and EOS levels in the diagnosis of AECOPD complicated with lung infection. Results: A total of 59 strains of pathogenic bacteria were isolated from 41 patients, including 41 strains of Gram-negative bacteria (69.49%), 16 strains of Gram-positive bacteria (27.12%) and 2 strains of fungi (3.39%). Among the Gram-negative bacteria, Klebsiella Pneumoniae and Pseudomonas Aeruginosa were highly resistant to Cefuroxime, Levofloxacin and Ampicillin. And among the Gram-positive bacteria, Staphylococcus Aureus and Streptococcus Pneumoniae were highly resistant to Penicillin, Gentamicin and Erythromycin. The levels of CRP, PCT and EOS in infected group were significantly higher than those in non-infected group ($P<0.05$); with the increase of pulmonary function grade, the levels of CRP, PCT and EOS were significant increased ($P<0.05$); and the levels of CRP, PCT and EOS were negatively correlated with the FEV1/FVC ratio ($P<0.05$). ROC curve results show that the levels of CRP, PCT and EOS have high clinical value in the diagnosis in patients of AECOPD complicated with pulmonary infection (all AUC>0.7). Conclusion: Gram-negative bacteria are the main bacteria in AECOPD complicated with pulmonary infection, and drugs should be used rationally according to the results of antimicrobial susceptibility test. The levels of CRP, PCT and EOS increased significantly and were closely related to pulmonary function, and thus have obvious clinical value in the diagnosis of AECOPD complicated with pulmonary infection.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease, pulmonary infection, eosinophil, procalcitonin, C-reactive protein

Introduction

Chronic obstructive pulmonary disease (COPD) is a common lung disease with highly destructiveness and longer course, which is characterized by persistent airflow limitation. It can cause irreversible damage to the lungs with a high fatality rate [1-3]. At present, the pathogenesis of COPD is not clear, but the condition is characterized by recurrent attacks and progressive progress. The 1-2 times of acute exacerbation per year experienced by most of COPD patients is also the leading cause of death. Studies have shown that infection is one of the risk factors leading to acute exacerbation of COPD. Therefore, in addition to alleviating the condition of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), it is also necessary to actively control the infection. Exploring the biological

indicators for early evaluation of infection also shows great clinical significance [4-7]. In recent years, a few studies have found that the existence of eosinophil (EOS) inflammation in COPD patients, suggests that EOS can be used as one of the biomarkers of COPD. However, there are very few reports about EOS expression in AECOPD patients complicated with pulmonary infection [8-10]. Procalcitonin (PCT) and C-reactive protein (CRP), as infectious markers, play an important role in the identification of infectious diseases such as bacterial or viral infection [11-13]. Based on this, this study aims to explore the expression of EOS, PCT and CRP in patients with AECOPD complicated with lung infection, aiming to provide relevant evidence for the clinical diagnosis and treatment of AECOPD complicated with pulmonary infection.

Materials and methods

Baseline data

A total of 167 patients with AECOPD treated in Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine from January 2017 to December 2019 were divided into infection group (n=41) and non-infection group (n=126). The diagnostic criteria of patients in the infection group referred to the relevant standards established by the Infectious Diseases Society of America (IDSA) in 2016 [14]. All patients informed consent and signed the consent form. This study was approved by the Ethics Committee of Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine.

Inclusion and exclusion criteria

Inclusion criteria: (1) All patients meet the relevant diagnostic criteria of the Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease [15]; (2) Patients aged between 20-85 years old; (3) Patients without immune disease; (4) Patients without severe hepatorenal function diseases; (5) Patients did not receive other treatment before admission; (6) The ratio of forced expiratory volume in one second/forced vital capacity (FEV1/FVC) <70%.

Exclusion criteria: (1) Patients that complicated with other serious diseases or infections; (2) Patients with neurological or mental diseases; (3) Patients who were participating in other studies; (4) Patients had organic lesions in the lung; (5) Patients had poor compliance.

Methods

Pathogen identification and drug resistance analysis: The sputum samples of the infection group were collected and inoculated into the sterile culture flasks, which was submitted for examination immediately. The samples were streak inoculated on the blood plate culture medium (Guangdong Huankai Microbiological Technology Co., Ltd., China). Some special samples should be inoculated on the broth medium (Shijiazhuang Seamer Technology Co., Ltd., China), and then streak inoculated on the blood plate culture medium. After incubated at 37°C for 24-72 hours, the bacteria were preliminarily identified according to the results of Gram staining and colony characteristics, and finally identified by the automatic microbial identification instrument (Beckman Coulter Co., Ltd., USA). The quality control bacteria were Staphylococcus aureus (ATCC25923), Staphylococcus epidermidis (ATCC12228) and Klebsiella pneumoniae (ATCC70060), all of which were purchased from the laboratory of Chinese Center for Disease Control and Prevention. GN2011 method was used for antimicrobial susceptibility test of Gram-positive bacteria, GP method was used for antimicrobial susceptibility test of Gram-negative bacteria, and disk diffusion method was used for antimicrobial susceptibility test [16].

Detection of serum PCT, CRP and EOS levels: Each 5 mL×2 tubes of venous blood were drawn from all patients when they were enrolled before receiving any treatment. One tube of the venous blood was centrifuged at 3000 r/min for 5 min to separate the serum. Then the serum CRP level was detected by immunoturbidimetric method (AU400 automatic biochemical analyzer, Olympus, Japan), and the PCT level was detected by enzyme-linked immunofluorescence method (ELISA, Spectra-Max-Paradigm multifunctional microplate reader, Molecular Devices, United States). The other tube was used for detection of EOS levels by a fully automatic biochemical analyzer (Hitachi, Japan). All the kits were purchased from Shanghai Beyotime Biotechnology Co., Ltd.

Pulmonary function grading: Grading criteria: Grade I, FEV1 ≥80% of the expected value; Grade II, FEV1 accounts for 50%-80% of the predicted value; Grade III, FEV1 accounts for less than 50% of the expected value [15].

Table 1. Comparison of baseline data between the two groups

Index	Infection group (n=41)	Non-infection group (n=126)	t/χ^2	P
Age (years)	64.5±3.4	64.1±3.7	0.613	0.541
Gender (n)			0.053	0.818
Male	22	65		
Female	19	61		
History of hypertension (n)			0.937	0.333
Yes	15	36		
No	26	90		
Complicated with diabetes (n)			2.805	0.094
Yes	16	32		
No	25	94		
Use of prophylactic antimicrobials			0.014	0.907
Yes	18	54		
No	23	72		
Mechanical ventilation			0.331	0.565
Yes	12	43		
No	29	83		

Table 2. Distribution of pathogens in the infection group

Pathogenic Bacteria	Strains (n=59)	Constituent ratio (%)
Gram-negative bacteria	41	69.49
Klebsiella pneumoniae	14	23.73
Pseudomonas aeruginosa	12	20.34
Acinetobacter baumannii	8	13.56
Enterobacter aerogenes	5	8.47
Escherichia coli	2	3.39
Gram-positive bacteria	16	27.12
Staphylococcus aureus	8	13.56
Streptococcus pneumoniae	5	8.47
Staphylococcus epidermidis	3	5.08
Fungus	2	3.39
Candida	2	3.39

Outcomes measurement

Main outcomes: PCT, CRP and EOS levels in the infected and non-infected groups; CRP, PCT and EOS levels in patients with different pulmonary function levels; The clinical value of ROC curve analysis of CRP, PCT and EOS levels in the diagnosis of AECOPD complicated with pulmonary infection.

Secondary outcomes: Pathogenic analysis and antimicrobial susceptibility test of patients in the infection group; The correlation between CRP, PCT and EOS levels and FEV1/FVC ratio in the infection group.

Statistical analysis

SPSS 22.0 was used for statistical analysis, and the measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd). Variance analysis was used for comparison of measurement data among multiple groups, and the t test was used for comparison between two groups. The counting data were expressed by the number of cases/percentage (n%), and it was compared by χ^2 test. Perason correlation was used to analyze the correlation, and ROC curve was used to analyze the clinical value of PCT, CRP and EOS in the diagnosis of AECOPD complicated with pulmonary infection. $P<0.05$ is considered statistically significant.

Result

Comparison of the baseline data between the two groups

The results showed that there was no significant difference in the baseline data such as age and gender between the two groups ($P>0.05$), as shown in **Table 1**.

Distribution of pathogens in infection group

The results showed that a total of 59 strains of pathogenic bacteria were isolated from 41 patients, including 41 strains of Gram-negative bacteria (69.49%), 16 strains of Gram-positive bacteria (27.12%) and 2 strains of fungi (3.39%), as shown in **Table 2** and **Figure 1**.

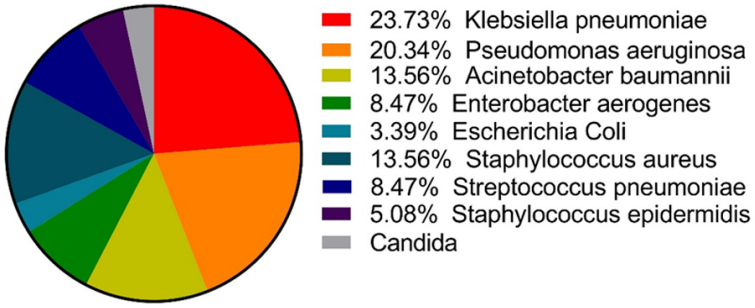

Figure 1. Distribution of pathogens in the infection group.

Table 3. Results of drug resistance of major Gram-negative bacteria

Antibacterials	Klebsiella pneumoniae (n=14)		Pseudomonas aeruginosa (n=12)	
	Strains	Drug resistance rate (%)	Strains	Drug resistance rate (%)
Cefuroxime	13	92.86	10	83.33
Levofloxacin	12	85.71	7	58.33
Ampicillin	12	85.71	9	75.00
Cefuroxime	7	50.00	5	41.67
Cefotaxime	5	35.71	3	25.00
Ceftazidime	3	21.43	1	8.33
Meropenem	1	7.14	0	0.00
Ciprofloxacin	0	0.00	0	0.00
Imipenem	0	0.00	1	8.33

Table 4. Results of drug resistance of major Gram-positive bacteria

Antibacterials	Staphylococcus aureus (n=8)		Streptococcus pneumoniae (n=5)	
	Strains	Drug resistance rate (%)	Strains	Drug resistance rate (%)
Penicillin	7	87.50	5	100.00
Gentamicin	7	87.50	5	100.00
Erythromycin	6	75.00	3	60.00
Clindamycin	5	62.50	2	40.00
Tetracycline	5	62.50	2	40.00
Rifampicin	3	37.50	2	40.00
Moxifloxacin	2	25.00	1	20.00
Levofloxacin	1	12.50	0	0.00
Vancomycin	0	0.00	1	20.00
Teicoplanin	0	0.00	0	0.00

The antibacterials resistance of major Gram-positive and Gram-negative bacteria

The results showed that Klebsiella pneumoniae and Pseudomonas aeruginosa were highly resistant to cefuroxime, levofloxacin and ampicillin among Gram-negative bacteria, while Staphylococcus aureus and Streptococcus pneumoniae were highly resistant to penicillin, gentamicin and erythromycin in Gram-positive bacteria, as shown in **Tables 3**, **4**.

Comparison of PCT, CRP and EOS levels between the two groups

The results showed that the levels of CRP, PCT and EOS in the infected group were significantly higher than those in the non-infected group (P<0.001). See **Table 5** for detail.

Comparison of PCT, CRP and EOS levels in patients with different pulmonary function grades in infection group

The results showed that compared with the grade I group, the levels of CRP, PCT and EOS in the grades of II and III groups were significantly higher, and compared with the grade II group, the CRP, PCT and EOS levels in the grade III group were significantly higher (P< 0.05). See **Table 6** for detail.

Correlation between the levels of PCT, CRP, EOS and FEV1/FVC ratio in infected group

The results showed that the levels of PCT, CRP and EOS were negatively correlated with the ratio of FEV1/FVC in the infection group (P<0.05), as shown in **Table 7**.

Results of ROC curve

The results showed that PCT has a higher diagnostic value when the cut-off value is 1.817 μg/L (AUC=0.878); CRP has a higher diagnostic value when the cut-off value is 18.292 mg/L (AUC=0.850); EOS has a certain diagnostic

Table 5. Comparison of PCT, CRP and EOS levels between the two groups

Groups	PCT (μg/L)	CRP (mg/L)	EOS (%)
Infection group (n=41)	3.22±1.87	20.15±8.66	3.37±1.17
Non-infection group (n=126)	0.86±0.75	9.13±5.32	2.16±1.01
t	11.589	9.737	6.437
P	<0.001	<0.001	<0.001

Note: EOS: eosinophil; PCT: procalcitonin; CRP: C-reactive protein.

Table 6. Comparison of PCT, CRP and EOS levels in patients with different pulmonary function grades in infection group

Groups	PCT (μg/L)	CRP (mg/L)	EOS (%)
Grade I (n=12)	2.01±1.09	13.52±6.69	2.19±0.83
Grade II (n=19)	3.32±1.54*	19.94±8.51*	3.32±1.21*
Grade III (n=10)	4.39±1.89*,#	26.85±9.02*,#	4.51±1.07*,#
F	6.793	7.258	12.635
P	0.003	0.002	<0.001

Note: Compared with Grade I, *P<0.05; compared with Grade II, #P<0.05. EOS: eosinophil; PCT: procalcitonin; CRP: C-reactive protein.

Table 7. Correlation between the levels of PCT, CRP, EOS and FEV1/FVC ratio in infected group

Statistics	PCT (μg/L)	CRP (mg/L)	EOS (%)
r	-0.564	-0.338	-0.417
P	<0.001	0.003	0.021

Note: EOS: eosinophil; PCT: procalcitonin; CRP: C-reactive protein; FEV1/FVC: forced expiratory volume in one second/forced vital capacity.

value (AUC=0.780) when the cutoff value is 2.963%, as shown in **Table 8** and **Figure 2**.

Discussion

This study showed that the Gram-negative bacteria were the major pathogens of AECOPD complicated with pulmonary infection, and among which the Klebsiella pneumoniae (23.73%) and Pseudomonas aeruginosa (20.34%) accounted for the highest proportion. Respiratory tract is the most common site of pathogen infection of AECOPD, which might be due to the weakening of alveolar elasticity, the attenuation of bronchial ciliary motility, and the difficulty of exclusion of lung secretions in patients with AECOPD. Besides, the immune function of patients is also weakened, resulting in an increased risk of infection of this kind of pathogens. Among Gram-positive bacteria, the infection rates of Staphylococcus aureus and Streptococcus pneumoniae were also higher (13.56% and 8.47%), which may be related to invasive operation, long-term use of antibiotics and other factors [17]. The results of drug resistance showed that all bacteria had certain drug resistance, suggesting that drugs should be used rationally according to the patient's condition.

PCT is mainly secreted by thyroid C cells. Under normal physiological conditions, the level of PCT is very low. Once infection occurs, a large amount of PCT is secreted by liver macrophages and monocytes under the stimulation of endotoxin and other factors, resulting in a significant increase in serum PCT level, and reached the peak at 12-24 hours after infection [18, 19]. Studies have shown that the increase of PCT level is mainly caused by bacterial infection or endotoxin and inflammatory factors that released by bacteria. However, the viral infection or other factors do not often cause the increase of PCT level, so it is considered to have high clinical value in the diagnosis of pulmonary bacterial infection [20]. The results of this study showed that the PCT level in AECOPD patients complicated with pulmonary infection increased significantly and closely related to the severity of lung function, which was consistent with the results of related studies. The results of ROC curve showed that when the cutoff value was 1.817 μg/L, the AUC of PCT in the diagnosis of AECOPD complicated with pulmonary infection was 0.878, suggesting that PCT could be used as one of the auxiliary diagnostic indicators in the diagnosis of AECOPD complicated with pulmonary infection. CRP is a kind of acute phase reactive protein, which has the characteristics of early appearance and rapid increase. When infectious occur, the level of CRP will increase in varying degrees. Studies have also shown that when infection occurs, CRP as a sensitive indicator of systemic inflammatory response, the level of which will increase significantly, and the change is often not affected by radiotherapy/chemotherapy drugs and hormone drugs [21]. The level of CRP in

Table 8. Results of ROC curve

Index	Cutoff value	AUC	95% CI	Sensitivity	Specificity	Positive predictive value	Negative predictive value	P
PCT (μg/L)	1.817	0.878	0.811, 0.946	0.732	0.881	0.666	0.910	<0.001
CRP (mg/L)	18.292	0.850	0.780, 0.921	0.659	0.921	0.730	0.893	<0.001
EOS (%)	2.963	0.780	0.698, 0.862	0.659	0.786	0.500	0.877	<0.001

Note: EOS: eosinophil; PCT: procalcitonin; CRP: C-reactive protein.

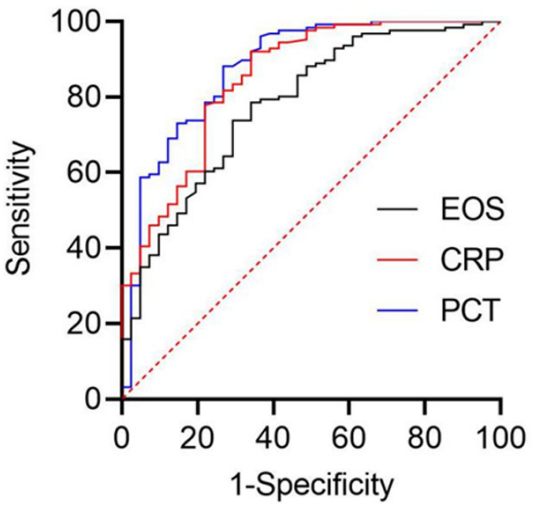

Figure 2. Results of ROC curve. EOS: eosinophil; PCT: procalcitonin; CRP: C-reactive protein.

patients with bacterial pneumonia is usually significantly increased, and it is believed to be closely related to the severity of the disease [22]. Indeed, this study showed that the level of CRP in patients with AECOPD complicated pulmonary infection was significantly higher than that in patients with simple AECOPD, and it is related to the severity of pulmonary function. The results of ROC curve showed that when the cutoff value was 18.292 mg/L, the AUC of PCT in the diagnosis of AECOPD with infection was 0.850, suggesting that it has a certain diagnostic value. Studies have shown that during the acute phase of COPD, local inflammatory stimulation promotes the exudation of a large number of inflammatory cells, which in turn leads to damage to lung tissue and causes airway remodeling [16]. Therefore, patients with acute exacerbation of COPD are extremely sensitive to clinical indicators. Previous studies have found a significant increase in EOS levels in sputum and bronchial biopsies in patients with AECOPD [23]. Studies have also confirmed that the invasion of eosinophilic inflammation is often closely related to the acute exacerbation of viral infections, however it's correlation with bacterial infections is not yet clear [24]. The results of this study showed that the level of EOS in peripheral blood of patients with pulmonary infection was significantly higher than that of patients with simple AECOPD, and the worse the pulmonary function of the patients, the higher the level of EOS. The study further found that when the cut-off value was 2.963%, the AUC of EOS in the diagnosis of AECOPD complicated with pulmonary infection was 0.780, suggesting that it has a certain clinical value.

To sum up, Gram-negative bacteria are the main causes of AECOPD complicated with pulmonary infection, and drugs should be used rationally according to the results of drug sensitivity. The levels of CRP, PCT and EOS were increased significantly in patients, and they were closely related to pulmonary function. CRP, PCT and EOS have certain clinical value in the diagnosis of AECOPD complicated with pulmonary infection. However, the sample source used in this study is a single center, and the changes of various indicators have not been dynamically observed. Therefore, follow-up studies are still needed for further verification.

Disclosure of conflict of interest

None.

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References

[1] Buhl R, Magder S, Bothner U, Tetzlaff K, Voß F, Loaiza L, Vogelmeier CF and McGarvey L. Long-term general and cardiovascular safety of tiotropium/olodaterol in patients with moder-

ate to very severe chronic obstructive pulmonary disease. Respir Med 2017; 122: 58-66.
[2] Brightling CE. Chronic obstructive pulmonary disease phenotypes, biomarkers, and prognostic indicators. Allergy Asthma Proc 2016; 37: 432-438.
[3] Mizumura K, Maruoka S, Gon Y, Choi AM and Hashimoto S. The role of necroptosis in pulmonary diseases. Respir Investig 2016; 54: 407-412.
[4] Nikolić E, Brandmajer T, Bokan V, Ulyashova M and Rubtsova M. Prevalence of escherichia coli resistant to beta-lactam antibiotics among patients with chronic obstructive pulmonary disease and urinary tract infection. Tohoku J Exp Med 2018; 244: 271-277.
[5] Protasov AD, Zhestkov AV, Kostinov MP, Shteiner ML, Tezikov YV, Lipatov IS, Yastrebova NE, Kostinova AM, Ryzhov AA and Polishchuk VB. Analysis of the effectiveness and long-term results of formation of adaptive immunity in the use of various medications and vaccination schemes against pneumococcal infection in patients with chronic obstructive pulmonary disease. Ter Arkh 2017; 89: 165-174.
[6] Li Y, Xie L, Xin S and Li K. Values of procalcitonin and C-reactive proteins in the diagnosis and treatment of chronic obstructive pulmonary disease having concomitant bacterial infection. Pak J Med Sci 2017; 33: 566-569.
[7] Wright AK, Newby C, Hartley RA, Mistry V, Gupta S, Berair R, Roach KM, Saunders R, Thornton T, Shelley M, Edwards K, Barker B and Brightling CE. Myeloid-derived suppressor cell-like fibrocytes are increased and associated with preserved lung function in chronic obstructive pulmonary disease. Allergy 2017; 72: 645-655.
[8] Garudadri S and Woodruff PG. Targeting chronic obstructive pulmonary disease phenotypes, endotypes, and biomarkers. Ann Am Thorac Soc 2018; 15 Suppl 4: S234-S238.
[9] Zysman M, Deslee G, Caillaud D, Chanez P, Escamilla R, Court-Fortune I, Nesme-Meyer P, Perez T, Paillasseur JL, Pinet C, Jebrak G, Roche N and Burgel PR. Relationship between blood eosinophils, clinical characteristics, and mortality in patients with COPD. Int J Chron Obstruct Pulmon Dis 2017; 12: 1819-1824.
[10] Hastie AT, Martinez FJ, Curtis JL, Doerschuk CM, Hansel NN, Christenson S, Putcha N, Ortega VE, Li X, Barr RG, Carretta EE, Couper DJ, Cooper CB, Hoffman EA, Kanner RE, Kleerup E, O'Neal WK, Paine R 3rd, Peters SP, Alexis NE, Woodruff PG, Han MK, Meyers DA and Bleecker ER; SPIROMICS investigators. Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort. Lancet Respir Med 2017; 5: 956-967.
[11] Kordek A, Torbé A, Tousty J, Łoniewska B, Podraza W, Nikodemski T and Rudnicki J. The determination of procalcitonin concentration in early-onset neonatal infection. Clin Pediatr (Phila) 2017; 56: 333-340.
[12] Wu G, Wu G, Wu SH and Wu HB. Comparison of procalcitonin guidance-administered antibiotics with standard guidelines on antibiotic therapy in children with lower respiratory tract infections: a retrospective study in China. Med Princ Pract 2017; 26: 316-320.
[13] Khattab AA, El-Mekkawy MS, Shehata AM and Whdan NA. Clinical study of serum interleukin-6 in children with community-acquired pneumonia. Egyp Pediat Assoc Gaz 2018; 66: 43-48.
[14] Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, Srinivasan A, Dellit TH, Falck-Ytter YT, Fishman NO, Hamilton CW, Jenkins TC, Lipsett PA, Malani PN, May LS, Moran GJ, Neuhauser MM, Newland JG, Ohl CA, Samore MH, Seo SK and Trivedi KK. Implementing an antibiotic stewardship program: guidelines by The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016; 62: e51-e77.
[15] Chronic Obstructive Lung Disease Group, Respiratory Disease Branch and Chinese Medical Associaition. Guidelines for the diagnosis and treatment of chronic obstructive pulmonary disease (2013 Revision). Front Med China (Electronic) 2014; 6: 67-80.
[16] Wang H, Chen MJ and Xu YC. A brief introduction of NCCLS disk diffusion method (Continued; December 1994 Edition). Zhonghua Jian Yan Yi Xue Za Zhi 1995; 18: 26-34.
[17] Restrepo MI and Reyes LF. Pneumonia as a cardiovascular disease. Respirology 2018; 23: 250-259.
[18] Sager R, Kutz A, Mueller B and Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. BMC Med 2017; 15: 15.
[19] Tan TL, Gomez MM, Kheir MM, Maltenfort MG and Chen AF. Should preoperative antibiotics be tailored according to patient's comorbidities and susceptibility to organisms? J Arthroplasty 2017; 32: 1089-1094, e1083.
[20] Aïssou L, Sorbets E, Lallmahomed E, Goudot FX, Pop N, Es-Sebbani S, Benouda L, Nuel G and Meune C. Prognostic and diagnostic value of elevated serum concentration of procalcitonin in patients with suspected heart failure. A review and meta-analysis. Biomarkers 2018; 23: 407-413.

[21] Neuville M, Vinclair C, Cally R and Bouadma L. Place of biomarkers in the management of pulmonary infections. Rev Mal Respir 2019; 36: 405-414.
[22] Piek A, Du W, de Boer RA and Silljé HHW. Novel heart failure biomarkers: why do we fail to exploit their potential? Crit Rev Clin Lab Sci 2018; 55: 246-263.
[23] Bafadhel M, Davies L, Calverley PM, Aaron SD, Brightling CE and Pavord ID. Blood eosinophil guided prednisolone therapy for exacerbations of COPD: a further analysis. Eur Respir J 2014; 44: 789-791.
[24] Kolsum U, Donaldson GC, Singh R, Barker BL, Gupta V, George L, Webb AJ, Thurston S, Brookes AJ, McHugh TD, Wedzicha JA, Brightling CE and Singh D. Blood and sputum eosinophils in COPD; relationship with bacterial load. Respir Res 2017; 18: 88.