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左氧氟沙星联合舒利迭对慢性阻塞性肺疾病急性加重期患者血清 SAA、TGF-β1、copeptin、sICAM-1 水平的影响 *

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摘要 目的:探讨左氧氟沙星联合舒利迭吸入对慢性阻塞性肺疾病急性加重期(AECOPD)患者血清淀粉样蛋白 A(SAA)、转化生长因子 -β1(TGF-β1)、羟基端糖肽(copeptin)、可溶性细胞黏附因子 -1(sICAM-1)水平的影响。**方法:**选择我院 2014 年 12 月 ~2016 年 12 月收治的 92 例 AECOPD 患者并按抽签法分为对照组和实验组,每组 46 例。对照组接受常规治疗,实验组基于对照组加以左氧氟沙星联合舒利迭吸入治疗。比较两组临床疗效,致力前后血清 SAA、TGF-β1、copeptin、sICAM-1、二氧化碳分压($PaCO_2$)、氧分压(PaO_2)、第 1 秒用力呼气容积(FEV1)、肺活量(FVC)、临床症状积分的变化及不良反应的发生情况。**结果:**治疗后,实验组临床总有效率选择高于对照组(P<0.05)。两组治疗后血清 SAA、TGF-β1、copeptin、sICAM-1、$PaCO_2$、临床症状积分均较治疗前显著下降,且实验组以上指标均明显低于对照组(P<0.05);两组治疗后 PaO_2、FEV1、FVC 均叫治疗前明显上升,且实验组以上指标均显著高于对照组(P<0.05)。两组不良反应的发生率比较差异无统计学意义(P>0.05)。**结论:**左氧氟沙星联合舒利迭吸入对 AECOPD 患者的临床效果明显优于常规治疗,能够降低患者血清 SAA、TGF-β1、copeptin、sICAM-1 水平,改善肺功能。

关键词:慢性阻塞性肺疾病急性加重期;左氧氟沙星;舒利迭吸入;淀粉样蛋白 A;转化生长因子 -β1;羟基端糖肽;可溶性细胞黏附因子 -1

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Effects of Levofloxacin combined with Seretide on the Serum SAA, TGF-β1, Copeptin, and sICAM-1 Levels of Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease*

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ABSTRACT Objective: To investigate the effects of levofloxacin and seretide on the serum levels of amyloid A (SAA), transforming growth factor-β1 (TGF-β1), hydroxyl glycopeptide (copeptin) and soluble cell adhesion factor-1 (sICAM 1) in patients with the acute exacerbation of chronic obstructive pulmonary disease (AECOPD). **Methods:** 92 cases of AECOPD who were treated in our hospital from December 2014 to December 2016 were selected and randomly divided into the control group and the experimental group. The control group was treated with routine method, while the experimental group was treated with levofloxacin and seretide based on control group. Then the clinical curative effect, the serum levels of SAA, TGF-β1, copeptin and sICAM-1, the partial pressure of carbon dioxide ($PaCO_2$), oxygen partial pressure (PaO_2), forced expiratory volume at the first second (FEV1) and forced vital capacity (FVC), clinical symptoms integral and incidence of adverse reactions were observed and compared between two groups. **Results:** After treatment, the total effective rate of experimental group was more effective than that of the control group (P<0.05). The serum levels of SAA, TGF-β1, copeptin, sICAM 1 and $PaCO_2$, the clinical symptom score of two group significantly decreased than those before treatment, which were significantly lower in the experimental group than those of the control group (P<0.05). The PaO_2, FEV1 and FVC of two group increased than those before treatment, which were higher in the experimental group than those of the control group (P<0.05). The incidence of adverse reactions showed no difference between the two groups (P>0.05). **Conclusion:** Levofloxacin and seretide was effective in the treatment of AECOPD, which can reduce the serum SAA, TGF-β1, copeptin and sICAM 1 levels and improve the lung function.

Key words: Acute exacerbation of chronic obstructive pulmonary disease; Levofloxacin; Seretide; Amyloid A; Transformation of growth factor-β1; Hydroxy end peptide; Soluble cell adhesion factor-1

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前言

慢性阻塞性肺疾病(COPD)作为肺部一种破坏性疾病，主要特征为气流受限且不全部可逆，并伴程度不一的炎症反应，多由慢性支气管扩张及慢性支气管炎等进展所致，空气污染、吸烟、感染等是其主要诱因[1]。胸闷、喘息、呼吸困难等是慢性阻塞性肺疾病的主要症状，其中急性加重期的病情危急，病情进展快速，可引起呼吸衰竭、心力衰竭等多种并发症，对患者生命安全形成显著影响[2]。COPD 的发病机制较为复杂，研究表明 SAA、TGF-β1、copeptin、sICAM-1 是导致肺部发生炎症病变的主要细胞因子，可参与机体系列病理生理改变，通过测定其浓度改变能够评估疾病转归[3,4]。

COPD 疾病急性加重期(AECOPD)患者目前多进行糖皮质激素、抗感染、吸氧等对症治疗，由于抗生素的不规范应用，引起耐药菌明显增加，降低临床疗效[5]。临床研究显示合理的抗菌疗法可提高此类患者的疗效，左氧氟沙星是喹诺酮一种代表药物，其抗菌谱比较广泛，且抗菌能力比较强[6]。Viana RCTP 等[7]研究显示舒利迭吸入对 AECOPD 患者可起到较好的临床效果，但国内鲜有关于二者联合治疗的报道。本研究主要探讨了左氧氟沙星联合舒利迭吸入对 AECOPD 患者血清 SAA、TGF-β1、copeptin、sICAM-1 水平的影响。

1 资料与方法

1.1 一般资料

选择我院 2014 年 12 月 ~2016 年 12 月收治的 92 例 AECOPD 患者，入选标准：符合 COPD 相关诊断标准[8]：慢性咳痰、咳嗽比气流受限出现的时间早，肺部 X 线胸片提示可有肺部紊乱、增粗等变化、也可见肺气肿，第 1 秒用力呼气容积 / 用量肺活量在 0.7 以下、气流存在受限、无法全部逆转，急性加重期[9]：咳嗽及呼吸急促加重、脓痰及咳痰量增多，运动耐量降低，呼吸道感染是急性加重的唯一诱因；无肺部其他疾病；心肝肾等主要脏器无严重异常；无恶性肿瘤。排除严重呼吸衰竭、近期有免疫抑制剂使用史，急性创伤或者感染，免疫系统异常，糖皮质激素相关禁忌症者。按抽签法将所有患者分为对照组和实验组，每组 46 例。对照组 20 例女，26 例男；年龄 51~71 岁，平均(64.29± 1.06)岁。实验组 24 例女，22 例男；年龄 50~72 岁，平均(64.95± 1.15)岁。两组基础资料比较差异均无统计学意义(P>0.05)，存在互比性。

1.2 治疗方法

对照组接受平喘、祛痰、抗感染、维持电解质平衡、控制性吸氧、支气管舒张药等基础治疗。实验组基于对照组加以左氧氟沙星及舒利迭吸入治疗，静脉注射 100 mL 左氧氟沙星注射液，每天进行 1 次；吸入两揿舒利迭，每日进行两次。两组均持续治疗 10 天，于用药结束时评估疗效，并统计期间不良反应的发生情况。

1.3 观察指标

1.3.1 **疗效观察** 临床控制：症状和体征消失，未见实验室指标异常，生活无需外界帮助；显效：症状及体征显著减轻，实验室指标基本无异常；好转：症状和体征有一定缓解，可见部分实验室指标异常；无效：症状和体征无变化甚者加重，临床控制、显效、好转均视作有效[10]。

1.3.2 **临床症状积分观察** 喘息：喘息状态为重度，患者难以平稳、活动受限，对患者睡眠及日常生活已产生显著影响计作 3 分；病情程度在重度及轻度之间计作 2 分；安静休息时或者停止活动后偶尔可见喘息，程度较轻，未对患者睡眠及日常生活形成影响计作 1 分；未见喘息表现计作 0 分。咳嗽：昼夜咳嗽频繁且剧烈，对患者睡眠及日常生活产生显著影响计作 3 分；病情程度在重度及轻度之间计作 2 分；轻微、间断性咳嗽，对患者睡眠及日常生活产生显著影响计作 1 分；偶尔或者未见咳嗽计作 0 分。哮鸣音：哮鸣音发作频繁计作 3 分；散在哮鸣音计作 2 分；偶尔可见哮鸣音计作 1 分；未见哮鸣音计作 0 分[11]。

1.3.3 **指标测定** 于用药前及结束时抽取患者 2 mL 晨期静脉血，将其常规分离后于低温环境中保存待检。血清 SAA、TGF-β1、copeptin、sICAM-1 选用酶联免疫法进行。选用动脉血气分析仪测定二氧化碳分压($PaCO_2$)、氧分压(PaO_2)。选用肺功能仪检测第 1 秒用力呼气容积(FEV1)、肺活量(FVC)。

1.4 统计学分析

选用 SPPS18.0 进行本研究的数据处理，计量资料以($\bar{x}\pm s$)表示，组间比较选用 t 检验进行，用[(例)%]表示计数资料，组间比较用 x^2 检验，以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后，实验组的总有效率为 93.47%，显著高于对照组(83.72%，P<0.05)，见表 1。

表 1 两组临床疗效的比较[例(%)]

Table 1 Comparison of the curative effect between two groups[n(%)]

Group	Clinical control	Effective	Improve	Invalid	Effective rate
Control group(n=46)	2(4.35)	10(21.74)	24(52.17)	10(21.74)	36(83.72)
Experimental group(n=46)	5(10.87)	24(52.17)	14(30.43)	3(6.52)	43(93.48)[a]

Note: Compared with the control group, [a]P<0.05.

2.2 两组治疗前后血清 SAA、TGF-β1、copeptin、sICAM-1 水平的比较

治疗前，两组血清 SAA、TGF-β1、copeptin、sICAM-1 水平比较差异无统计学意义(P>0.05)；治疗后，两组血清 SAA、TGF-β1、copeptin、sICAM-1 均较治疗前显著下降，且实验组以上指标明显低于对照组(P<0.05)，见表 2。

2.3 两组治疗前后血气分析指标及肺功能指标的比较

治疗前，两组血气分析指标及肺功能指标比较差异均无统

计学意义(P>0.05)；治疗后，两组 $PaCO_2$ 均较治疗前明显下降，且实验组显著低于对照组(P<0.05)，两组 PaO_2、FVC、FEV1 均叫治疗前明显上升，且实验组以上指标明显高于对照组(P<0.05)，见表 3。

表 2 两组治疗前后血清 SAA、TGF-β1、copeptin、sICAM-1 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the Serum SAA, TGF-β1, copeptin, sICAM-1 levels between two groups before and after the treatment($\bar{x}\pm s$)

Group	Time	SAA(μ g/L)	TGF-β1(μg/L)	Copeptin(ng/L)	sICAM-1(μg/L)
Control group(n=46)	Before treatment	153.90± 19.12	1186.59± 148.70	365.42± 45.68	9.17± 1.13
	After treatment	31.96± 4.08[b]	803.70± 100.95[b]	138.65± 17.23[b]	8.18± 1.09[b]
Experimental group(n=46)	Before treatment	150.64± 19.95	1183.20± 147.29	369.27± 44.19	9.23± 1.50
	After treatment	25.19± 3.11 [ab]	645.59± 80.64 [ab]	116.49± 14.52 [ab]	5.86± 0.73 [ab]

Note: Compared with control group [a]P<0.05; Compared with before treatment [b]P<0.05.

表 3 两组治疗前后血气分析指标及肺功能指标的比较($\bar{x}\pm s$)

Table 3 Comparison of the blood gas analysis index and pulmonary function index between two groups before and after the treatment($\bar{x}\pm s$)

Groups	Time	$PaCO_2$(mmHg)	PaO_2(mmHg)	FVC(L)	FEV1(L)
Control group(n=46)	Before treatment	50.59± 6.23	51.08± 6.70	1.19± 0.15	0.96± 0.12
	After treatment	41.20± 5.13[b]	65.37± 8.37[b]	1.41± 0.18[b]	1.25± 0.15[b]
Experimental group(n=46)	Before treatment	51.39± 6.88	51.53± 6.13	1.22± 0.17	0.93± 0.13
	After treatment	35.42± 4.20[ab]	74.30± 9.25[ab]	1.67± 0.21[ab]	1.36± 0.17[ab]

Note: Compared with control group, [a]P<0.05; Compared with before treatment, [b]P<0.05.

2.4 两组治疗前后临床症状积分的比较

治疗前，两组临床症状积分比较差异无统计学意义(P>0.05)；治疗后，两组临床症状积分均较治疗前明显下降，且实验组以上指标明显低于对照组(P<0.05)，见表 4。

表 4 两组治疗前后临床症状积分的比较($\bar{x}\pm s$)

Table 4 Comparison of the clinical symptoms integral between two groups before and after the treatment($\bar{x}\pm s$)

Groups	Time	Wheezing(points)	Cough(points)	Wheeze(points)
Control group(n=46)	Before treatment	1.78± 0.22	2.76± 0.34	2.09± 0.25
	After treatment	0.85± 0.11[b]	1.52± 0.18[b]	1.02± 0.13[b]
Experimental group (n=46)	Before treatment	1.75± 0.24	2.71± 0.36	2.16± 0.23
	After treatment	0.64± 0.08 [ab]	1.15± 0.14 [ab]	0.88± 0.11 [ab]

Note: Compared with control group [a]P<0.05; Compared with before treatment [b]P<0.05.

2.5 两组不良反应发生情况的比较

两组均有头晕、皮疹及肝功能异常发生，组间不良反应发生率比较差异无统计学意义(P>0.05)，见表 5。

表 5 两组不良反应发生情况的比较[例(%)]

Table 5 Comparison of the incidence of adverse reactions between two groups[n(%)]

Group	Dizziness	Rash	Abnormal liver function	Adverse reaction rate
Control group(n=46)	3(6.52)	3(6.52)	1(2.17)	7(15.21)
Experimental group(n=46)	2(4.34)	2(4.34)	1(2.17)	5(10.87)

3 讨论

COPD 为呼吸系统的常见病变，其中急性加重期的住院率及病死率较高，临床以控制感染、缓解病情、减少病死率为治疗原则[12]。国外研究显示病毒或者细菌感染是 AECOPD 的主要诱因，能够参与机体的气道重构，降低肺功能，导致血氧供应不足，造成肺部的循环阻力出现上升、肺部动脉的高压状态，引起右心肥厚、扩大，导致患者发生呼吸衰竭、右心功能衰竭等，影响预后[13]。感染初期阶段，病灶细菌能够过度繁殖，引起明显的炎症反应，经静脉给药可使药物于短时间内作用于病变部位，从而避免细菌增殖[14]。

氟喹诺酮类抗生素由于抗菌谱广泛且活性强、生物后效应较明显，且半衰期长，为慢性阻塞性肺疾病急性加重期经验性抗感染的首选药物[15]。左氧氟沙星作为一种氟喹诺酮类药物的第 3 代药物，存在作用力强、抗菌谱广等优势，能够使细菌相关酶受到抑制，影响 DNA 复制，诱导病原菌凋亡、坏死[16]。近年来

研究显示革兰阴性菌为呼吸系统感染的主要病原菌,对于既往的抗生素有着较高的耐药性,左氧氟沙星对多数革兰阴性菌均可起到较高的杀伤力,且穿透力强,可广泛分布于组织体液中,到达支气管黏膜、肺泡巨噬细胞[17]。Torres-Sánchez I 等[18]研究报道 AECOPD 单接受左氧氟沙星抗感染治疗的效果并不理想,细菌清除率相对较低,需辅助其他药物。

舒利迭是 β2 受体激动剂与糖皮质激素的一种复方制剂,其中沙美特罗能够缓解组胺所致的支气管收缩,且可使支气管扩张,避免肥大细胞的生成,减轻气道高反应性[19]。丙酸氟替卡松可起到比较确切的抗炎作用,从而使哮喘症状缓解,且可减少全身性糖皮质激素的不良反应。以吸入的方式使药液经呼吸道给药,并于肺泡、黏膜等组织中发挥作用,局部吸入药物能直接作用于病灶组织,并于短时间内分布于肺泡管、毛细支气管等区域[20]。其次,吸入疗法能够以较小剂量起到最大治疗效果,药物吸收后多于肝脏内产生代谢,不良反应少,且操作比较简单[21]。本研究显示左氧氟沙星联合舒利迭吸入治疗后有效率显著高于常规治疗组,说明二者联合治疗能够提高临床疗效,且治疗后临床症状积分下降更为明显,考虑与二者可起到协同作用有关,但具体作用机制未完全明确。

AECOPD 时能够诱导机体产生内毒素及免疫复合物,并引起血管内皮细胞及单核巨噬细胞释放多种细胞因子,引起炎性因子的过度分泌,从而刺激机体的级联反应[22]。机体正常状态下,SAA 的含量较低,可作为一种急性时相蛋白从而诱导机体的炎症反应,外伤、炎症等刺激下其含量能够显著增加[23]。TGF-β1 是多肽生长因子,广泛分布于肾、肺等组织中,肺内可由淋巴细胞、嗜酸性粒细胞等生成,也可来自于气道上皮细胞。多种外界刺激能够导致气道产生炎症反应,引起气道的上皮出现损伤,增加 TGF-β 生成及分泌,使炎症反应加剧[24]。copeptin 为机体的时相蛋白,可直观反映机体组织的炎症状态,呼吸道病变时其浓度和病情呈正相关 [25]。AECOPD 患者由于气道阻塞,能够引起机体缺氧,加之细菌毒素及炎症因子等刺激激活大量内皮细胞,导致 sICAM-1 水平明显增加。sICAM-1 作为免疫球蛋白,是机体防御系统中的重要因子,多于神经细胞、血管内皮细胞中分布,能够诱导炎性细胞发生聚集,引起血管内皮受损加剧,加速疾病进展。本研究显示两组治疗前血清 SAA、TGF-β1、copeptin、sICAM-1 浓度明显上升,提示 AECOPD 有多种细胞因子参与,经治疗后两组上述指标均下降,但左氧氟沙星联合舒利迭吸入组下降更为明显,提示两者联合治疗更能有效调节细胞因子的分泌,缓解机体内环境状态,从而促进患者恢复。同时有研究发现 AECOPD 患者因气道高反应性及气道炎症、呼吸道纤毛对痰液的清除能力下降、痰液分泌增多等使气道内的黏液分泌物增加,导致痰液黏稠、且增多。同时患者由于呼吸比较急促,痰液难以咯出,使气道感染及阻塞加剧,引起肺功能减弱,导致血液中氧气浓度降低,并引起二氧化碳潴留,进一步加剧病情。此外,本研究结果显示两组治疗后血气分析指标及肺功能均有改善,但联合治疗组改善更为明显,进一步证实二者联合治疗的效果,且两组安全性均较可靠,仅少数患者出现些许不良反应,且症状较轻。

综上所述,左氧氟沙星联合舒利迭吸入对 AECOPD 患者的效果明显优于常规治疗,能够降低患者血清 SAA、TGF-β1、copeptin、sICAM-1 浓度,改善其肺功能。

参 考 文 献(References)

[1] Castillo A, Edriss H, Selvan K, et al. Characteristics of Patients With Congestive Heart Failure or Chronic Obstructive Pulmonary Disease Readmissions Within 30 Days Following an Acute Exacerbation[J]. Qual Manag Health Care, 2017, 26(3): 152-159

[2] Antus B, Drozdovszky O, Barta I. Assessment of exhaled carbon monoxide in exacerbations of chronic obstructive pulmonary disease [J]. Physiol Int, 2016, 103(2): 211-219

[3] Koul PA, Mir H, Akram S, et al. Respiratory viruses in acute exacerbations of chronic obstructive pulmonary disease [J]. Lung India, 2017, 34(1): 29-33

[4] Rahimirad S, Ghaffary MR, Rahimirad MH, et al. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acuteexacerbation of chronic obstructive pulmonary disease[J]. Tuberk Toraks, 2017, 65(1): 25-31

[5] Marsh B, Drake MG. Outpatient Management for Acute Exacerbations of Obstructive Lung Diseases [J]. Med Clin North Am, 2017, 101(3): 537-551

[6] Giusti M, Blasi F, Iori I, et al. Prulifloxacin vs Levofloxacin for Exacerbation of COPD after Failure of Other Antibiotics [J]. COPD, 2016, 13(5): 555-560

[7] Viana RCTP, Pincelli MP, Pizzichini E, et al. Chronic obstructive pulmonary disease exacerbation in the intensive care unit: clinical, functional and quality of life at discharge and 3 months of follow up [J]. Rev Bras Ter Intensiva, 2017, 29(1): 47-54

[8] Feetham L, van Dorn A. Chronic obstructive pulmonary disease (COPD)[J]. Lancet Respir Med, 2017, 5(1): 18-19

[9] Płusa T. Pathogenesis, diagnosis and treatment of chronic obstructive pulmonary disease in the light of new research [J]. Pol Merkur Lekarski, 2016, 41(246): 263-268

[10] Jouneau S, Dres M, Guerder A, et al. Management of acute exacerbations of chronic obstructive pulmonary disease (COPD). Guidelines from the Société de pneumologie de langue française (summary[J]. Rev Mal Respir, 2017, 34(4): 282-322

[11] Bergin SP, Rackley CR. Managing Respiratory Failure in Obstructive Lung Disease[J]. Clin Chest Med, 2016, 37(4): 659-667

[12] Khan A, Dickens AP, Adab P, et al. Self-management behaviour and support among primary care COPD patients: cross-sectional analysis of data from the Birmingham Chronic Obstructive Pulmonary Disease Cohort[J]. NPJ Prim Care Respir Med, 2017, 27(1): 46

[13] Lorenz J, Bals R, Dreher M, et al. Exacerbation of COPD [J]. Pneumologie, 2017, 71(5): 269-289

[14] Einvik G, Bhatnagar R, Holmedahl NH, et al. Premature Ventricular Complex is More Prevalent During Acute Exacerbated than Stable States ofChronic Obstructive Pulmonary Disease, and Is Related to Cardiac Troponin T[J]. COPD, 2017, 14(3): 318-323

[15] Furqan S, Paracha SA. Frequency of Streptococcus pneumonia and Haemophilus influenza in acute exacerbation ofchronic obstructive airway disease and their sensitivity to levofloxacin [J]. J Pak Med Assoc, 2014, 64(4): 399-402

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肌炎的临床研究[J].中药药理与临床, 2017, 33(1): 209-211
Chen Xi-ping. The clinical research of astragalus injection combined with Potassium Sodium Dehydroandrograpolide Succinate Injection in the treatment of hand foot mouth disease complicated with myocarditis in children [J]. Pharmacology and Clinics of Chinese Materia Medica, 2017, 33(1): 209-211

[20] 王磊,王军,刘树文,等.曲美他嗪对慢性心力衰竭患者血管内皮功能的影响[J].现代生物医学进展, 2017, 17(21): 4159-4162
Wang Lei, Wang Jun, Liu Shu-wen, et al. Effect of trimetazidine on vascular endothelial function in patients with chronic heart failure[J]. Progress in Modern Biomedicine, 2017, 17(21): 4159-4162

[21] Milinkoviċ I, Rosano G, Lopatin Y, et al. The Role of Ivabradine and Trimetazidine in the New ESC HF Guidelines[J]. Card Fail Rev,2016, 2(2): 123-129

[22] 刘帅,牛珩,张金国,等.黄芪注射液联合曲美他嗪治疗病毒性心肌炎疗效与安全性的 Meta 分析 [J]. 中国药房, 2015, 26(36): 5113-5116
Liu Shuai, Niu Heng, Zhang Jin-guo, et al. Meta-analysis of the Efficacy and Safety of Astragali Radix Injection Combined with Trimetazidine in the Treatment of Viral Myocarditis [J]. China Pharmacy, 2015, 26(36): 5113-5116

[23] 叶艳芳,李世林,于涛,等.黄芪注射液联合生脉饮治疗急性病毒性心肌炎的临床研究[J].中医学报, 2014, 30(7): 1034-1035, 1038
Ye Yan-fang, Li Shi-lin, Yu Tao, et al. Clinical Observation on Combination of Astragalus Injection and Sheng-mai Decoction in the Treatment of Acute viral Myocarditis [J]. China Journal of Chinese Medicine, 2014, 30(7): 1034-1035, 1038

[24] Aguirre JL, Jurado M, Porres-Aguilar M, et al. Acute nonrheumatic streptococcal myocarditis resembling ST-elevation acute myocardial infarction in a young patient[J]. Proc (Bayl Univ Med Cent), 2015, 28 (2): 188-190

[25] 王前军. 曲美他嗪联合黄芪注射液治疗急性病毒性心肌炎的临床疗效及安全性[J].临床合理用药, 2016, 9(9): 8-9, 12
Wang Qian-jun. Clinical effects and safety of trimetazidine combined with astragalus radix injection in treating acute viral myocarditis [J]. Chinese Journal of Clinical Rational Drug Use, 2016, 9(9): 8-9, 12

[26] Asymbekova EU, Sherstyannikova OM, Tugeeva EF. Clinical Case Demonstrating Use of Trimetazidine In the Treatment of Stable Angina[J]. Kardiologiia, 2016, 56(3): 101-103

[27] Gorbunova ML, Vilkova AV. Assessment of Efficacy and Safety of Metabolic Therapy With Trimetazidine MB in Patients With Ischemic Heart Disease and Chronic Heart Failure [J]. Kardiologiia, 2016, 56 (3): 67-72

[28] Glezer M, CHOICE-2 study investigators. Real-world Evidence for the Antianginal Efficacy of Trimetazidine from the Russian Observational CHOICE-2 Study[J]. Adv Ther, 2017, 34(4): 915-924

[29] Momen A, Ali M, Karmakar PK, et al. Effects of sustained-release trimetazidine on chronically dysfunctional myocardium of ischemic dilated cardiomyopathy - Six months follow-up result[J]. Indian Heart J, 2016, 68(6): 809-815

[30] Hatton JL, Bhat PK, Gandhi S. Clozapine-induced myocarditis: recognizing a potentially fatal adverse reaction [J]. Tex Heart Inst J, 2015, 42(2): 155-157

(上接第 712 页)

[16] Mohan A, Arora S, Uniyal A, et al. Evaluation of plasma leptin, tumor necrosis factor-α, and prealbumin as prognostic biomarkers during clinical recovery from acute exacerbations of chronic obstructive pulmonary disease[J]. Lung India, 2017, 34(1): 3-8

[17] Murphy PB, Rehal S, Arbane G, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial[J]. JAMA, 2017, 317(21): 2177-2186

[18] Torres-Sánchez I, Cruz-Ramírez R, Cabrera-Martos I, et al. Results of Physiotherapy Treatments in Exacerbations of Chronic Obstructive Pulmonary Disease: A Systematic Review [J]. Physiother Can, 2017, 69(2): 122-132

[19] Koul PA, Mir H, Akram S, et al. Respiratory viruses in acute exacerbations of chronic obstructive pulmonary disease [J]. Lung India, 2017, 34(1): 29-33

[20] Yip E, Karimi S, Pien LT. Evaluation of a Therapeutic Interchange from Fluticasone/Salmeterol to Mometasone/Formoterol in Patients with Chronic Obstructive Pulmonary Disease [J]. J Manag Care Spec Pharm, 2016, 22(4): 316-323

[21] Davis JR, Kern DM, Williams SA, et al. Health Care Utilization and Costs After Initiating Budesonide/Formoterol Combination orFluticasone/Salmeterol Combination Among COPD Patients New to ICS/LABA Treatment [J]. J Manag Care Spec Pharm, 2016, 22(3): 293-304

[22] Andrijevic L, Milutinov S, Andrijevic I, et al. Association Between the Inflammatory Biomarkers and Left Ventricular Systolic Dysfunction in Patients with Exacerbations of Chronic Obstructive Pulmonary Disease[J]. Balkan Med J, 2017, 34(3): 226-231

[23] Mahmood MQ, Reid D, Ward C, et al. Transforming growth factor (TGF) β₁ and Smad signalling pathways: A likely key to EMT-associated COPD pathogenesis [J]. Respirology, 2017, 22 (1): 133-140

[24] Yilman M, Erenler AK, Baydin A. Copeptin: a diagnostic factor for critical patients [J]. Eur Rev Med Pharmacol Sci, 2015, 19 (16): 3030-3036

[25] Bender BG, Hernandez Vecino RA, McGrath K, et al. Comparative Analysis of Persistence to Treatment among Patients with Asthma or COPD Receiving AirFluSal Forspiro or Seretide Diskus Salmeterol/Fluticasone Propionate CombinationTherapy [J]. JAllergy Clin Immunol Pract, 2016, 4(5): 884-889