

doi: 10.13241/j.cnki.pmb.2021.11.009

• 临床研究 •

噻托溴铵辅助治疗呼吸窘迫综合征对血清 NO
与 VEGF 水平的影响研究 *高琳 李倩 王丽 雷靖 谭焰[△]

(南京医科大学附属南京医院呼吸内科 江苏 南京 210000)

摘要 目的: 探讨与研究噻托溴铵辅助治疗呼吸窘迫综合征对血清一氧化氮 (Nitric oxide, NO) 与血管内皮生长因子 (vascular endothelial growth factor, VEGF) 水平的影响。**方法:** 2016 年 9 月到 2020 年 9 月选择在本院进行急诊的呼吸窘迫综合征患者 84 例, 根据随机数字表法把患者分为噻托溴铵组与对照组各 42 例。对照组给予鼻塞式持续气道正压通气治疗, 噻托溴铵组在对照组治疗的基础上给予噻托溴铵治疗, 两组都治疗观察 2 w, 检测血清 NO 与 VEGF 表达变化情况。**结果:** 治疗后噻托溴铵组的总有效率为 97.6%, 高于对照组的 85.7% ($P < 0.05$)。两组治疗后的氧合指数高于治疗前 ($P < 0.05$), 噻托溴铵组高于对照组 ($P < 0.05$)。两组治疗后的 FEV₁ 与 FVC 值高于治疗前 ($P < 0.05$), 噻托溴铵组高于对照组 ($P < 0.05$)。两组治疗后的血清 NO 值高于治疗前 ($P < 0.05$), 血清 VEGF 值低于治疗前 ($P < 0.05$), 噻托溴铵组与对照组对比差异也都有统计学意义 ($P < 0.05$)。**结论:** 噻托溴铵辅助治疗呼吸窘迫综合征能抑制血清 VEGF 的表达与促进 NO 的释放, 改善患者的肺功能与氧合状况, 从而提高治疗效果。

关键词: 噻托溴铵; 呼吸窘迫综合征; 肺功能; 氧化指标; 血管内皮生长因子; 一氧化氮

中图分类号: R563.8 **文献标识码:** A **文章编号:** 1673-6273(2021)11-2045-04

Effects of Tiotropium Bromide in Adjuvant Treatment of
Respiratory Distress Syndrome on Serum NO and VEGF Levels*GAO Lin, LI Qian, WANG Li, LEI Jing, TAN Yan[△]

(Department of Respiratory Medicine, Nanjing Hospital Affiliated to Nanjing Medical University, Nanjing, Jiangsu, 210000, China)

ABSTRACT Objective: To explore and study the effects of tiotropium bromide adjuvant treatment of respiratory distress syndrome on serum nitric oxide (NO) and vascular endothelial growth factor (VEGF) levels. **Methods:** From September 2016 to September 2020, 84 cases of patients with respiratory distress syndrome were selected for emergency treatment in this hospital. All the cases were divided into tiotropium bromide group and control group with 42 cases each groups accorded to the random number table method. The control group were treated with nasal congestion continuous positive airway pressure, and the tiotropium bromide group were treated with tiotropium bromide on the basis of the control group. Both groups were treated and observed for 2 weeks, and serum NO and VEGF expression changes were detected. **Results:** After treatment, the total effective rates of the tiotropium bromide group were 97.6%, which were higher than 85.7% of the control group ($P < 0.05$). The oxygenation index of the two groups after treatment were higher than that before treatment ($P < 0.05$), and the tiotropium bromide group were higher than the control group ($P < 0.05$). The FEV₁ and FVC values of the two groups after treatment were higher than those before treatment ($P < 0.05$), and the tiotropium bromide group were higher than the control group ($P < 0.05$). The serum NO value of the two groups after treatment were higher than before treatment ($P < 0.05$), and the serum VEGF value were lower than before treatment ($P < 0.05$), the difference compared between the tiotropium bromide group and the control group were also statistically significant ($P < 0.05$). **Conclusion:** Tiotropium bromide adjuvant treatment of respiratory distress syndrome can inhibit the expression of serum VEGF and promote the release of NO, improve the patient's lung function and oxygenation status, thereby enhance the therapeutic effect.

Key words: Tiotropium bromide; Respiratory distress syndrome; Lung function; Oxidation index; Vascular endothelial growth factor; Nitric oxide

Chinese Library Classification (CLC): R563.8 **Document code:** A

Article ID: 1673-6273(2021)11-2045-04

前言

呼吸窘迫综合征是临床上的常见危重疾病, 发病患者具有

* 基金项目: 国家自然科学基金青年基金项目(81903089); 南京医科大学科技发展基金 - 一般项目 (NMUB2019165)

作者简介: 高琳 (1981-), 男, 本科, 主治医师, 研究方向: 呼吸相关及重症方向, 电话: 18951941227, E-mail: GL19810413@163.com

[△] 通讯作者: 谭焰 (1970-), 主任医师, 硕士, 研究方向: 呼吸与危重医学、重症感染, 电话: 18951941227, E-mail: tanyan1970@126.com

(收稿日期: 2021-01-04 接受日期: 2021-01-28)

极高的致残率及致死率,多伴有肺炎、低氧血症、肺源性心脏病等症状^[1]。有研究显示,尽管机械通气等治疗技术得到了显著改进,但是呼吸窘迫综合征在成人中1年死亡率依然在1/3左右。该病多需要进行急诊治疗,而单纯药物治疗对病情的缓解效果并不显著^[2,3]。随着现代医疗科技水平的不断发展,无创通气技术(Non-invasive Ventilation, NIV)已被广泛应用于临床实践当中,能显著减少呼吸机相关性并发症,减少镇静剂的用量,减轻患者气管插管等带来的痛苦^[4,5]。现常用的无创通气模式主要包括鼻塞式持续气道正压通气、双水平气道内正压通气、无创高频振荡通气、加温湿化高流量导鼻管通气等^[6,7]。其中鼻塞式持续气道正压通气可给予患者较稳定的呼吸支持,改善通气和氧合,缓解患者的痛苦,可显著改善肺的氧合功能,可有效清除二氧化碳,同时有效提高撤机成功率^[8,9]。噻托溴铵是一种选择性抗胆碱药,具有抑制腺体分泌及炎症反应的作用,也可通过作用于平滑肌M3受体而发挥支气管扩张作用^[10,11]。NO是体内重要的舒张因子,可诱导血管平滑肌细胞舒张^[12]。VEGF为一种血管通透因子,在直接调节蛋白通透性与多种器官系统血管功能中发挥重要作用^[13,14]。本研究探讨了噻托溴铵辅助治疗

呼吸窘迫综合征对血清NO与VEGF水平的影响,以明确噻托溴铵的应用价值与机制。现总结报道如下。

1 资料与方法

1.1 研究对象

2016年9月到2020年9月选择在本院进行急诊的呼吸窘迫综合征患者84例,纳入标准:临床资料完整;符合急性呼吸窘迫综合征的诊断标准;年龄20~70岁;患者或家属知情同意;本院伦理委员会批准了此次研究,具有机械通气与噻托溴铵使用指征;治疗前未使用过噻托溴铵治疗。排除标准:精神类疾病患者;合并其他呼吸系统疾病者;恶性肿瘤患者;妊娠期与哺乳期患者;临床资料缺乏者;治疗期间死亡者;妊娠期与哺乳期患者;肝、肾等器官存在功能性障碍患者;既往有肺部手术史者;过敏体质者;不配合本研究方案的患者。

根据随机数字表法把患者分为噻托溴铵组与对照组各42例,两组患者的心率、中心动脉压、APACHE II评分、性别、年龄、BMI等对比差异无统计学意义($P>0.05$),见表1。

表1 两组一般资料对比
Table 1 Comparison of two general data

Groups	n	Heart rate (sub/min)	Central arterial pressure (mmHg)	APACHE II score (score)	Gender (M/F)	Age (years)	BMI (kg/m ²)
Tiotropium bromide group	42	102.22±10.58	82.47±4.44	21.33±3.19	20/21	38.11±2.58	22.47±1.11
Control group	42	102.88±9.28	82.33±6.15	21.19±2.94	22/20	38.10±3.18	22.19±1.10

1.2 治疗方法

对照组:给予鼻塞式持续气道正压通气治疗,使用经鼻面罩双水平气道正压呼吸机(鱼跃医疗公司生产),患者取半卧位,戴头带及鼻面罩,保证患者以舒适的状态进行治疗。通气参数:S/T通气模式,吸气峰压(PIP)15~20 cmH₂O,呼气末正4~6 cmH₂O,维持血氧饱和度在90%以上,FiO₂ 0.3~0.6,在治疗过程中依据患者病情变化调节参数。每日需要通气2~3次,每次持续2~4 h。

噻托溴铵组:在对照组治疗的基础上给予噻托溴铵治疗,使用噻托溴铵粉吸入剂(Boehringer Ingelheim Pharma GmbH & CoKG,注册证号:H20160227,18 μg/揿)吸入器吸入,2揿/次,1次/d。

两组都治疗观察2 w,所有患者在治疗过程中都给予抗炎、化痰、吸氧、平喘等治疗。

1.3 观察指标

(1)疗效标准:显效:临床症状均明显缓解,肺通气及动脉血气分析明显改善;有效:临床症状有所缓解,肺通气及动脉血气

分析有所改善;无效:无达到上述标准甚或恶化。以(显效+有效)所占比例统计总有效率。(2)在治疗前后采用Chest-25F型肺功能仪测定患者的肺功能,包括FEV₁、FVC等。(3)在治疗前后采用全自动血气分析仪测定与计算氧合指数(PaO₂/FiO₂)。(4)在治疗前后采集患者的外周血2 mL,离心分离血清后,采用酶联免疫试剂盒检测血清NO与VEGF含量。试剂盒购自上海酶联生物科技有限公司,所有检测操作均严格按照说明书进行。

1.4 统计方法

使用IBM SPSS Statistics 24.0,符合正态分布的计量数据已($\bar{x} \pm s$)表示(对比为t检验),计数数据以%表示(对比 χ^2 分析),检验水准为 $\alpha=0.05$, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 总有效率对比

治疗后噻托溴铵组的总有效率为97.6%(41/42),高于对照组的85.7%(36/42),对比差异有统计学意义($P<0.05$),见表2。

表2 两组总有效率对比(例,%)
Table 2 Comparison of the total effective rate between the two groups (n, %)

Groups	n	Excellence	Effective	Invalid	Total effective rate
Tiotropium bromide group	42	37	4	1	41(97.6%)*
Control group	42	22	12	6	36(85.7%)

Note: Compared with the control group, * $P<0.05$.

2.2 氧合指数变化对比

治疗前,两组的氧合指数对比差异无统计学意义($P>0.05$),

治疗后,两组的氧合指数高于治疗前($P<0.05$),且噻托溴铵组高于对照组($P<0.05$),见表 3。

表 3 两组治疗前后氧合指数变化对比($\bar{x}\pm s$)

Table 3 Comparison of changes in oxygenation index between the two groups before and after treatment ($\bar{x}\pm s$)

Groups	n	Pretherapy	Post-treatment
Tiotropium bromide group	42	99.13 $\pm$ 3.19	172.00 $\pm$ 12.75 [#]
Control group	42	99.67 $\pm$ 2.58	137.92 $\pm$ 14.57 [#]

Note: Compared with the Pretherapy, [#] $P<0.05$; compared with the control group, * $P<0.05$.

2.3 肺功能变化对比

治疗前,两组的 FEV₁ 与 FVC 值对比差异无统计学意义

($P>0.05$),治疗后,两组的 FEV₁ 与 FVC 值高于治疗前($P<0.05$),且噻托溴铵组高于对照组($P<0.05$),见表 4。

表 4 两组治疗前后肺功能变化对比($\bar{x}\pm s$)

Table 4 Comparison of changes in lung function between the two groups before and after treatment ($\bar{x}\pm s$)

Groups	n	FEV ₁		FVC	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Tiotropium bromide group	42	2.21 $\pm$ 0.32	2.62 $\pm$ 0.11 [#]	1.31 $\pm$ 0.22	1.81 $\pm$ 0.25 [#]
Control group	42	2.18 $\pm$ 0.11	2.41 $\pm$ 0.17 [#]	1.30 $\pm$ 0.13	1.56 $\pm$ 0.22 [#]

Note: Compared with the Pretherapy, [#] $P<0.05$; compared with the control group, * $P<0.05$.

2.4 血清 NO 与 VEGF 含量变化对比

治疗前,两组的血清 NO、VEGF 值对比差异无统计学意义($P>0.05$),两组治疗后的血清 NO 值高于治疗前($P<0.05$),血清

VEGF 值低于治疗前($P<0.05$),且噻托溴铵组与对照组对比差异也都有统计学意义($P<0.05$),见表 5。

表 5 两组治疗前后血清 NO 与 VEGF 含量变化对比($\bar{x}\pm s$)

Table 5 Comparison of changes in serum NO and VEGF levels before and after treatment in the two groups ($\bar{x}\pm s$)

Groups	n	NO(μ mol/L)		VEGF(mg/L)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Tiotropium bromide group	42	23.29 $\pm$ 2.16	32.88 $\pm$ 3.711 ^{**}	133.26 $\pm$ 13.57	94.57 $\pm$ 10.57 ^{**}
Control group	42	23.19 $\pm$ 1.47	29.17 $\pm$ 2.75 [#]	132.76 $\pm$ 14.02	112.77 $\pm$ 12.77 [#]

Note: Compared with the Pretherapy, [#] $P<0.05$; compared with the control group, * $P<0.05$.

3 讨论

呼吸窘迫综合征是多种致病因素引起的肺部综合征,临床上以进行性低氧血症、非心源性肺水肿为特征。随着社会经济的发展与人民群众生活水平的提高,呼吸窘迫综合征危险因素流行趋势显著,导致了该病的发病率持续增加^[15,16]。机械通气是治疗呼吸窘迫综合征最重要的支持手段,无创通气通过建立人工气道,可有效避免患者受创,减少创伤性并发症的发生^[17]。不过临床传统采用高频通气方法也可能造成患者出现低氧血症、高碳酸血症等并发症,也不利于患者预后的持续改善^[18,19]。鼻塞式持续气道正压通气是一个简单、有效的呼吸支持模式,可在持续低水平正压通气的基础上给予每分钟设定次数的高压通气,可有效清除二氧化碳,也可显著改善肺的氧合功能^[20]。其也能提供持续的气道压力对保持肺支气管扩张有一定的机械性支撑作用,有效改善通气/血流比值,避免细支气管闭陷,增加功能残气量,从而提高氧分压和有效排出二氧化碳^[21,22]。但是采用无创通气仍需较高的吸入氧体积分数,不利于持续改善患者

的预后。本研究显示治疗后噻托溴铵组的总有效率为 97.6%,高于对照组的 85.7%;两组治疗后的氧合指数高于治疗前,噻托溴铵组高于对照组。从机制上分析,噻托溴铵能够缓解呼吸道平滑肌功能障碍、支气管痉挛,从而可改善患者氧合状况^[23,24]。特别是噻托溴铵能够降低肺通气阻力,有效舒张气道平滑肌从而优化肺通气功能^[25]。

肺内炎症、肺泡内皮细胞和上皮细胞损伤是引起呼吸窘迫综合征的重要因素,特别是大量分泌物在机体肺内积聚,使得患者肺部通气/血流失衡,导致吸入的氧气不能有效进入血液循环而致氧合功能障碍^[26,27]。无创通气有利于复张肺泡,改善氧合,减轻肺损伤。FEV₁、FVC 是临床应用广泛的肺通气指标,呼吸窘迫综合征患者普遍存在 FEV₁、FVC 水平降低,并且与病情严重程度、预后存在相关性^[28]。本研究显示两组治疗后的 FEV₁ 与 FVC 值高于治疗前,噻托溴铵组高于对照组。从机制上分析,噻托溴铵可选择性作用在 M1、M2 受体,其也属于强效抗胆碱能支气管舒张剂,能减少杯状细胞黏液分泌,降低患者咳嗽量,能降低胆碱能神经张力,可将气道静息阻力降低,从而使

狭窄的气道得到舒张,促使肺功能得到有效改善^[29,30]。

内皮损伤以及毛细血管通透性增加对呼吸窘迫综合征发生的调节作用已达成共识^[31]。在呼吸窘迫综合征发病患者肺损伤的早期,可趋化中性粒细胞,VEGF 可被释放进入血浆中,引发参与并介导肺部的炎症反应^[32]。而机体强烈的应激反应可使得 VEGF 沿着肺泡毛细血管膜的上皮细胞溢进内皮细胞,增加血管通透性,导致肺水肿的发生。NO 是由细胞一氧化氮合酶以 L-精氨酸为底物合成和释放的舒张因子之一,其具有舒张血管的功能,能减少基础和刺激后的内皮细胞迁移,也可抑制血小板粘附、聚集和白细胞粘附等,有利于重塑动脉血管。当 NO 表达量下降时,可导致血小板黏附、血栓形成和血管平滑肌细胞的异常增生,从而出现血管再狭窄^[33]。吸入 NO 可选择性地扩张通气区域的肺血管,提高氧分压,改善机体的通气/血流比值^[34]。本研究显示两组治疗后的血清 NO 值高于治疗前,血清 VEGF 值低于治疗前,噻托溴铵组与对照组对比差异也都具有统计学意义。从机制上分析,噻托溴铵会进一步减少肺内分流,可在短时间内改善低氧血症状况,可能对炎症侵袭后肺泡的修复发挥作用,从而抑制 VEGF 的表达与促进 NO 的释放^[35]。本研究也存在一定的不足,病例患者数量比较少,机制分析还不够深入,将在后续研究中深入分析。

总之,噻托溴铵能辅助治疗呼吸窘迫综合征,能抑制血清 VEGF 的表达与促进 NO 的释放,改善患者的肺功能与氧合状况,从而提高临床治疗效果。

参考文献(References)

- [1] Cassambai S, Mee CJ, Renshaw D, et al. Tiotropium bromide, a long acting muscarinic receptor antagonist triggers intracellular calcium signalling in the heart [J]. *Toxicol Appl Pharmacol*, 2019, 384(15): e114778
- [2] Désirée LL, Margarita FV, Mónica RG, et al. An online survey detected knowledge gaps and cost-saving opportunities in asthma maintenance treatment among allergists, pulmonologists, ENTs and primary care[J]. *World Allergy Organ J*, 2019, 12(12): 84-89
- [3] Domingo C, Rello J, Sogo A. As-needed ICS-LABA in Mild Asthma: What Does the Evidence Say?[J]. *Drugs*, 2019, 79(16): 1729-1737
- [4] Driessen MT, Whalen J, Buguth BS, et al. Correction to: Cost-effectiveness analysis of umeclidinium bromide/vilanterol 62.5/25 mcg versus tiotropium/olodaterol 5/5 mcg in symptomatic patients with chronic obstructive pulmonary disease: a Spanish National Healthcare System perspective[J]. *Respir Res*, 2019, 20(1): e18
- [5] Graham LM, Kerstjens HM, Vogelberg C, et al. Safety of tiotropium Respimat(?) in black or African-American patients with symptomatic asthma[J]. *Respir Med*, 2019, 155(22): 58-60
- [6] Hirata K, Ichinose M, Perry J, et al. Particle size and gastrointestinal absorption influence tiotropium pharmacokinetics: a pilot bioequivalence study of PUR0200 and Spiriva HandiHaler [J]. *Int J Chron Obstruct Pulmon Dis*, 2019, 85(3): 580-589
- [7] Hoogendoorn M, Corro Ramos I, Baldwin M, et al. Long-term cost-effectiveness of the fixed-dose combination of tiotropium plus olodaterol based on the DYNAGITO trial results [J]. *Int J Chron Obstruct Pulmon Dis*, 2019, 14(9): 447-456
- [8] Hoshino M, Akitsu K, Ohtawa J. Comparison between montelukast and tiotropium as add-on therapy to inhaled corticosteroids plus a long-acting β (2)-agonist in for patients with asthma [J]. *J Asthma*, 2019, 56(9): 995-1003
- [9] Ammari WG, Khalil Mohammad M, Tayyem RF. Evaluation of patients' real-world post-dispensing use and storage environments of tiotropium bromide Respimat? soft mist inhaler on its in vitro dose delivery and lung deposition[J]. *Pulm Pharmacol Ther*, 2019, 58(16): 1829-1833
- [10] Averell CM, Laliberté F, Duh MS. Characterizing Real-World Use Of Tiotropium In Asthma In The USA [J]. *Respir Res*, 2019, 12(11): 309-321
- [11] Berton DC, Marques RD, Palmer B, et al. Effects of lung deflation induced by tiotropium/olodaterol on the cardiocirculatory responses to exertion in COPD[J]. *Respir Med*, 2019, 157(14): 59-68
- [12] Kang JY. Expression of Muscarinic Receptors and the Effect of Tiotropium Bromide in Aged Mouse Model of Chronic Asthma[J]. *Can Respir J*, 2019, 82(1): 71-80
- [13] Kaplan A, Chapman KR, Anees SM, et al. Real-life effectiveness of indacaterol-glycopyrronium after switching from tiotropium or salmeterol/fluticasone therapy in patients with symptomatic COPD: the POWER study[J]. *Drug Dev Ind Pharm*, 2019, 14(14): 249-260
- [14] Blair HA. Tiotropium/Olodaterol: A Review in COPD [J]. *Drugs*, 2019, 79(9): 997-1008
- [15] Caillaud D, Costes F, Chalmet P, et al. Allergic Bronchopulmonary Candidiasis Mimicking COPD[J]. *Am J Med*, 2019, 132(11): 797-798
- [16] Calzetta L, Rogliani P, Page C, et al. Pharmacological characterization of the interaction between tiotropium bromide and olodaterol on human bronchi and small airways[J]. *Pulm Pharmacol Ther*, 2019, 56(12): 39-50
- [17] Casale TB, Aalbers R, Bleecker ER, et al. Tiotropium Respimat add-on therapy to inhaled corticosteroids in patients with symptomatic asthma improves clinical outcomes regardless of baseline characteristics [J]. *Int J Chron Obstruct Pulmon Dis*, 2019, 158(12): 97-109
- [18] Kawachi S, Fujimoto K. Efficacy of tiotropium and olodaterol combination therapy on dynamic lung hyperinflation evaluated by hyperventilation in COPD: an open-label, comparative before and after treatment study [J]. *Int J Chron Obstruct Pulmon Dis*, 2019, 14(9): 1167-1176
- [19] Kistemaker LEM, Elzinga CRS, Tautermann CS, et al. Second M(3) muscarinic receptor binding site contributes to bronchoprotection by tiotropium[J]. *Br J Pharmacol*, 2019, 176(16): 2864-2876
- [20] Maltais F, Hamilton A, Voß F, et al. Dose Determination for a Fixed-Dose Drug Combination: A Phase II Randomized Controlled Trial for Tiotropium/Olodaterol Versus Tiotropium in Patients with COPD[J]. *Respir Med*, 2019, 36(4): 962-968
- [21] Mansfield L, Duong-Quy S, Craig T. Burden of Asthma and Role of 2.5 μ g Tiotropium Respimat (®) as an Add-On Therapy: A Systematic Review of Phase 2/3 Trials [J]. *Adv Ther*, 2019, 36(10): 2587-2599
- [22] Martínez FJ, Abrahams RA, Ferguson GT, et al. Effects of baseline symptom burden on treatment response in COPD [J]. *Int J Chron Obstruct Pulmon Dis*, 2019, 14(9): 181-194

- [15] 张秀琴. 小儿肺炎支原体肺炎合并喘息的影响因素分析和诊疗对策[J]. 福建医药杂志, 2016, 38(6): 30-33
- [16] Lemanske RF Jr. Asthma in Childhood: Expression, Exacerbation, and Progression[J]. J Allergy Clin Immunol Pract, 2016, 4(1): 36-37
- [17] Hayes D Jr, Nance AE, Mansour HM. Sigh Syndrome in Pediatric Asthma[J]. Lung, 2019, 197(1): 111-112
- [18] Ghaffari J. The prevalence of children's asthma: A few comments[J]. Clin Respir J, 2018, (9): 2454
- [19] Klion AD, Rothenberg ME. Advances in eosinophilic diseases in 2018[J]. J Allergy Clin Immunol, 2019, 144(6): 1490-1494
- [20] 郭靖, 刘亚楠, 郝明明, 等. 哮喘患儿合并肺炎支原体感染免疫状态及 Th1/Th2 平衡的变化 [J]. 中华医院感染学杂志, 2020, 30(9): 1412-1416
- [21] 张奕, 刘长山. 呼出气一氧化氮及外周血嗜酸性粒细胞水平在儿童肺炎支原体肺炎中的临床意义[J]. 天津医科大学学报, 2019, 25(2): 147-149
- [22] Cantorna MT, Snyder L, Arora J. Vitamin A and vitamin D regulate the microbial complexity, barrier function, and the mucosal immune responses to ensure intestinal homeostasis [J]. Crit Rev Biochem Mol Biol, 2019, 54(2): 184-192
- [23] Zmijewski MA. Vitamin D and Human Health [J]. Int J Mol Sci, 2019, 20(1): 145
- [24] Tangpricha V, Lukemire J, Chen Y, et al. Vitamin D for the Immune System in Cystic Fibrosis (DISC): a double-blind, multicenter, randomized, placebo-controlled clinical trial [J]. Am J Clin Nutr, 2019, 109(3): 544-553
- [25] Martineau AR, Jolliffe DA, Greenberg L, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis[J]. Health Technol Assess, 2019, 23(2): 1-44
- [26] Wolsk HM, Harshfield BJ, Laranjo N, et al. Vitamin D supplementation in pregnancy, prenatal 25 (OH)D levels, race, and subsequent asthma or recurrent wheeze in offspring: Secondary analyses from the Vitamin D Antenatal Asthma Reduction Trial [J]. J Allergy Clin Immunol, 2017, 140(5): 1423-1429, e5
- [27] 兰允昌, 杨嘉, 杨仲央, 等. 小儿支原体肺炎合并哮喘的免疫功能及维生素 D 水平监测分析 [J]. 中国医师杂志, 2018, 20(5): 781-783
- [28] 张娟, 田伟, 代宝春, 等. 肺炎支原体肺炎患儿血清维生素 D 水平及其对免疫功能的影响[J]. 儿科药学杂志, 2020, 26(1): 4-6
- [29] 任彦红, 陈丹, 张广超, 等. 血清 25 羟维生素 D、YKL-40 检测在诊治儿童难治性支原体肺炎中的临床意义 [J]. 医学研究杂志, 2019, 48(2): 121-126
- [30] Mathyssen C, Gayan-Ramirez G, Bouillon R, et al. Vitamin D supplementation in respiratory diseases: evidence from randomized controlled trials[J]. Pol Arch Intern Med, 2017, 127(11): 775-784

(上接第 2048 页)

- [23] Meng JF, Li H, Luo MJ, et al. Efficacy of tiotropium in treating patients with moderate-to-severe asthma: A meta-analysis and systematic review based on 14 randomized controlled trials [J]. Medicine (Baltimore), 2019, 98(33): e16637
- [24] Moretz C, Bengtson LG, Sharpsten L, et al. Evaluation of rescue medication use and medication adherence receiving umecclidinium/vilanterol versus tiotropium bromide/olodaterol [J]. Int J Chron Obstruct Pulmon Dis, 2019, 14: 2047-2060
- [25] Murphy KR, Chipps BE. Tiotropium in children and adolescents with asthma[J]. Ann Allergy Asthma Immunol, 2020, 124(3): 267-276
- [26] Muttray A, Schneider M, Roßbach B. Urine tropenol ester levels in workers handling tiotropium bromide synthesis: implications for exposure prevention and biomonitoring [J]. Arh Hig Rada Toksikol, 2019, 70(2): 118-122
- [27] Neri T, Scalise V, Passalacqua I, et al. Tiotropium inhibits proinflammatory microparticle generation by human bronchial and endothelial cells[J]. Sci Rep, 2019, 9(1): 11631
- [28] Palli SR, Buikema AR, Ducharme M, et al. Costs, exacerbations and pneumonia after initiating combination tiotropium olodaterol versus triple therapy for chronic obstructive pulmonary disease [J]. J Bras Pneumol, 2019, 8(15): 1299-1316
- [29] Ridolo E, Pellicelli I, Gritti B, et al. Patient-reported outcomes and considerations in the management of COPD: focus on indacaterol/glycopyrronium bromide [J]. Patient Prefer Adherence, 2019, 13: 145-150
- [30] Rogliani P, Cazzola M, Calzetta L. Cardiovascular Disease in Chronic Respiratory Disorders and Beyond [J]. J Am Coll Cardiol, 2019, 73(17): 2178-2180
- [31] Sethi S, Kerwin E, Watz H, et al. AMPLIFY: a randomized, Phase III study evaluating the efficacy and safety of aclidinium/formoterol vs monocomponents and tiotropium in patients with moderate-to-very severe symptomatic COPD [J]. Int J Chron Obstruct Pulmon Dis, 2019, 14(14): 667-682
- [32] Sobradillo Ecenarro P, García-Rivero JL, López Caro JC. Bronchodilator therapy in the prevention of COPD exacerbations[J]. Semergen, 2019, 45(7): 479-488
- [33] Steinmetz KO, Abenhardt B, Pabst S, et al. Assessment of physical functioning and handling of tiotropium/olodaterol Respimat (®) in patients with COPD in a real-world clinical setting [J]. Br J Clin Pharmacol, 2019, 14(9): 1441-1453
- [34] Szeffler SJ, Vogelberg C, Bernstein JA, et al. Tiotropium Is Efficacious in 6- to 17-Year-Olds with Asthma, Independent of T2 Phenotype[J]. J Allergy Clin Immunol Pract, 2019, 7(7): 2286-2295
- [35] Szpak R, Strapasson GC. Legal demands of the tiotropium bromide for treatment of chronic obstructive pulmonary disease and their financial impact for the State of Paraná, Brazil [J]. N Engl J Med, 2020, 18(9): e4442