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浅谈急性高原病的发生发展机制及预防和治疗的最新研究进展

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摘　要

上升至海拔高于2500米以上的高原地区可能会发生高原反应。高原环境中空气稀薄，大气压和氧分压低，紫外线照射强，早晚温差大、天气恶劣。随着海拔的升高，空气越来越稀薄，导致空气中氧含量亦逐渐减少，当出现高原反应时如不及时干预可能会引起高原肺水肿，甚至高原脑水肿，严重时威胁生命。近年来，随着我国旅游业、经济的日渐发展，我们与高海拔地区的接触也越来越多，并认识到高原病的研究格为重要，因此使研究高原病的发生发展机制及预防和治疗的热潮成为研究热点。本文章中讨论急性高原病(AMS)相关心血管疾病相关的发生发展机制及预防和治疗的防治基本趋势，旨在能够快速地了解到高原病的相关信息及研究状况，同时也为高原病的进一步研究提供理论参考。

关键词

急性高原病，心血管病，发生发展机制，预防，治疗

The Latest Research Progress on the Occurrence and Development Mechanism, Prevention and Treatment of Acute Mountain Sickness

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Abstract

Altitude sickness can occur in high altitude areas above 2500 meters. In the plateau environment, the air is thin, the atmospheric pressure and oxygen partial pressure are low, the ultraviolet radiation is strong, the temperature difference between morning and evening is large, and the weather is bad. With the increase of altitude, the air becomes thinner and thinner, resulting in a gradual reduction of oxygen content in the air. If timely intervention is not provided, altitude sickness may cause altitude pulmonary edema or even altitude brain edema, which may threaten life in serious cases. In recent years, with the increasing development of tourism and economy in China, we have more and more contact with the high altitude area, and realize that the research on plateau disease is important, so it is the hot research topic of the occurrence and development mechanism of plateau disease, prevention and treatment. This article discusses the occurrence and development mechanism of acute mountain sickness (AMS) related cardiovascular diseases and the basic trend of prevention and treatment, aiming to quickly understand the relevant information and research status of AMS, and also provide theoretical reference for further research on AMS.

Keywords

Acute Mountain Sickness, Cardiovascular Disease, Mechanism of Occurrence and Development, Prevention, Treatment

1. 前言

高原地区由于空气稀薄、氧分压低，人体进入高海拔地区后出现缺氧。由于个体对缺氧的耐受性不同，引起的病理生理反应也有差别。身处海拔高于 2500 米尤其高于 4000 米以上的人群、肥胖人群以及既往有偏头痛病史的人群患高原反应的风险更大[1] [2]。

2. 高原病发生发展机制

高原病根据发生的急缓分为慢性高原病和急性高原病。急性高原病可分为急性高原反应、急性肺水肿、急性脑水肿等三种类型。缺氧诱导因子(Hypoxia Inducible Factor, HIF)是缺氧反应当中的关键因素，HIF 是一种异二聚体复合物，调节糖酵解酶、血管内皮生长因子(Vascular Endothelial Growth Factor, VEGF)和促红细胞生成素等几千个基因的表达，除此之外，热休克蛋白 70 和 NO (一氧化氮)等的表达亦影响不同人群对缺氧的耐受性[3]。AMS 发生的主要决定因素为海拔高度、个体敏感度、爬升速度、停留时间、体力消耗程度和适应程度[4] [5]，Webb JD 等研究表明高原适应以 HIF-1 的表达上调来实现[6]。总之 AMS 的患病率在很大程度上取决于个体差异及环境因素。

正常状态下细胞内的氧约有 80%~90%在线粒体内通过氧化磷酸化过程参与生成 ATP，轻度缺氧或缺氧初期，线粒体提高氧利用度以增强呼吸功能。严重缺氧或随着缺氧时间的增加，线粒体外氧的利用出现障碍，即神经介质的生成及生物转化过程降低，继而引起线粒体呼吸功能降低，ATP 生成减少，严重时引起线粒体肿胀、嵴崩解、外膜破裂和基质外溢等病变并导致细胞功能障碍，引起炎症反应。Minabino.T 等研究证明缺氧在血管壁结构改变之前就可以在肺中引起明显的炎症[7]。长期处于炎症反应，引起 ROS

的产生增加、NO 生物利用度降低，从而引起内皮细胞功能障碍，并伴有平滑肌细胞增殖和肺小动脉壁中基质沉积，导致血管内皮细胞调节血管张力和结构功能的受损[8]，久之慢性缺氧会导致肺动脉高压，脑水肿，高原病等。肺动脉压持续增高使右心负荷加重，引起右心室肥大，即为高原性心脏病，属于肺源性心脏病范畴[9]。缺氧又可引起继发性红细胞增多增加[10] [11]，血液粘稠度增加，进一步加重心脏负荷。缺氧还刺激血儿茶酚胺、垂体加压素和肾上腺皮质激素分泌增加，肾素－血管紧张素－醛固酮系统活性增强使血压升高，进一步加重高原性心脏病[12]。此外急性缺氧可引起急性高原病(Acute Mountain Sickness, AMS)。

AMS 由非特异性症状组成，这些症状通常出现在≥2500 m 的未适应高原环境个体中，多在到达新海拔 4~12 小时后出现，且于新海拔地区度过第一个晚上后最为明显，采取适当的措施后，症状会逐渐消失[13]。AMS 主要症状是头痛，在高海拔地区，低氧环境引起的脑血管扩张导致脑血流量增加和脑血容量增加，从而导致头痛[14]。头疼为最常用的诊断 AMS 所必需的症状，然而，有学者认为大致有 5% AMS 患者因以非头疼为症状而漏诊[8]-[15]，其余症状包括食欲不振、恶心、头晕、疲倦乏力和失眠。这些症状均为非特异性，尤其是失眠在高海拔地区的健康人中非常普遍[11]。若头痛、恶心等症状进展，且对一线止吐和止痛药反应性差，以及随着疲劳程度的增加，可能出现 AMS 向 HACE (高原脑水肿)或 HAPE (高原肺水肿)的进展[16]。HAPE 是一种非心源性肺水肿[17]，以咳嗽、进行性呼吸困难和运动耐力下降为特点，一般在抵达高海拔地区后 2~4 天内出现[18]，1 周后发生率低[19]。缺氧性肺动脉高压，它可能至少通过三种潜在机制介导：肺一氧化氮合成障碍；内皮素-1 合成过度；交感神经激活过度等，肺泡上皮钠转运也存在缺陷[20]，最终导致肺水肿。HACE 的主要症状为智力受损、嗜睡、昏迷和共济失调。昏迷可能在共济失调或精神状态改变后 24 小时内出现[21]。如果没有适当的治疗，HACE 通常会导致死亡，严重时可导致在发病后 24 小时内死亡[22]。

3. 高原病的预防与治疗

进入高原前，应先进行有关高原环境特点、生活注意事项及高原病防治知识等方面的教育。若攀登者有较严重的器质性疾病，严重神经衰弱或呼吸道感染等疾病，暂不宜进入高原地区以免出现机体不良反应。研究表明适当食入碳水化合物后可以减轻 AMS 的症状，增加活动耐力[23]。Consolazio CF，Golja P 等人研究表明，在急性缺氧暴露期间，摄入碳水化合物可以改善动脉氧合[24] [25]。

攀登高原前进行预防性锻炼。进入高原过程中，坚持阶梯升高原则，缓慢攀登可减少 AMS 发生率[26]。在需要攀爬至 3000 米以上时，建议每天爬升速度不超过 300 米，每爬升 1000 米休息一天[27]。如果不能阶梯上升，于攀登前 24 小时预防性服用乙酰唑胺。乙酰唑胺对 AMS 已知病史或快速上升到 2500 米以上海拔的人群有利[28]。

1) 吸氧：如出现 AMS 相关症状，通过经鼻导管和面罩吸氧(1~2 L/min)后，可以明显缓解缺氧症状[29]。进入高原后避免剧烈运动，以免动脉血氧饱和度进一步降低，注意防冻保暖，避免烟酒和服用镇静催眠药[30] [31]。如出现严重的 AMS 应立即吸入氧气治疗，并尽快下降 300 米以上[27]。

2) 乙酰唑胺：乙酰唑胺通过抑制碳酸酐酶，减少肾脏对碳酸氢盐的重吸收，导致碳酸氢盐利尿和代谢性酸中毒，从而增加呼吸频率和加快适应速度，使 PaO_2 更高。其推荐的预防性用药计量存在较多的争议，van Patot MC 及 Basnyat B 等研究发现在攀登前 8 到 24 小时开始 125 毫克每天两次口服可有效降低 AMS 发生率，并且使用此较低剂量可将副作用降至最低[32] [33]。该药应在机体到达稳定海拔高度后继续使用两天，或在持续上升时继续使用。如果 AMS 的症状随着上升到更高的海拔而再次出现，则加量至 125 毫克每天两次口服。从大量研究中发现确定乙酰唑胺的最佳剂量并非易事。许多研究都涉及不同海

拔高度和攀登速率的受试者。一项荟萃分析得出 750 毫克/天可预防 AMS，但较低剂量则不能减少 AMS 的发生率[34]。然而有学者认为因为不同的攀登速率被放在一起分析，另一方面，250 毫克/天与 750 毫克/天的有效试验可能对非易感个体有选择偏见，因此此研究结果未能全面被接受[35]。一项小剂量乙酰唑胺(125 毫克每日两次口服)也被证明可以降低 AMS 的发病率和严重程度[32]，这结论与另一份研究相矛盾，该研究发现乙酰唑胺 500 毫克/天口服可有效降低 AMS 的发生率，而 250 毫克/天口服则不能有效降低其发生率[36]。在海拔高度迅速上升到 2500 米以上的人群中，乙酰唑胺可将 AMS 的发病率降低约 75% [37]。尽管有其他几种药物可供选择，但乙酰唑胺仍然是预防 AMS 的主要药物。乙酰唑胺可能有几种副作用，包括头痛和恶心[38]。更多的亲水性碳酸酐酶抑制剂，如苯乙酰胺，可能会有较少的中枢神经系统副作用。一项由 Collier DJ 等进行的比较苯乙酰胺与乙酰唑胺在预防 AMS 的研究发现苯乙酰胺队列中的副作用较少[39]。但这一结论仍需要进一步验证。

3) 地塞米松：地塞米松是预防 AMS 的有效药物，但其潜在的副作用较多。地塞米松可用于磺胺类药物过敏或乙酰唑胺不耐受患者，亦可于救援人员被要求非常快地上升时使用。预防剂量为 2 mg 每 6 小时口服或 4 毫克每 12 小时一次口服，于上升当天开始口服 2 天或在海拔迅速上升时口服以预防 AMS 等的发生[28] [40]。

4) 布地奈德：在一项由 Chen GZ 等进行的实验研究中发现吸入布地奈德亦可有效预防 AMS。在这实验中，参与者于攀登高原前 3 天每天两次吸入 200 mg 布地奈德，最终发现地奈德使 AMS 的发生率相对于安慰剂降低了 36%，与同一研究中口服地塞米松的降低 AMS 发生率相当[41] [42]。地塞米松与布地奈德需要从经济、便捷等方面进一步评估。

5) 利尿药：利尿药可以减少肺血管外积液；然而，利尿剂在高原肺水肿(HAPE)治疗中作用不明显，特别是因为许多 HAPE 患者同时存在血管内容量减少，因此 HAPE 患者实用利尿药可能存在一定的风险[43]。

6) 硝苯地平：多项研究和广泛的临床经验都证明了硝苯地平可以预防易感人群的肺源性高原病，但少数个体可能会发生低血压。2019 年美国野外医学会实践指南一 AMS 的预防和治疗指南建议：推荐使用硝苯地平预防易感人群 HAPE 的发生，硝苯地平缓释片使用方法为 30 g/次，每 12 小时 1 次，或 20 mg/次，每 8 小时 1 次[44]。此外沙美特罗/丙酸氟替卡松干粉剂为长效 β 受体激动剂与吸入型糖皮质激素的复方制剂，两者在炎症和支气管痉挛方面有明显的互补作用，具有强效的抗炎和持续的支气管扩张作用。国内对沙美特罗/丙酸氟替卡松干粉剂在支气管哮喘治疗方面的报道较多，而在 AMS 防治方面的报道还较少，尚未列入 AMS 常规治疗中，有必要进一步探讨[45]。他达拉非一项小样本的研究发现他达拉非可有效预防易感人群高原性肺水肿的发生。与硝苯地平相比，他达拉非的使用缺乏临床经验。对于不适合使用硝苯地平的易感人群可以使用他达拉非预防高原肺水肿，建议使用剂量为 10 mg/次，每 12 小时 1 次[46] [47]。

7) 布洛芬：Gertsch JH、Lipman GS 等进行的两项试验表明，布洛芬(每天 3 次，600 毫克)在预防 AMS 方面比安慰剂更有效[48] [49]，而由 Lundeberg J 等进行的规模较小的研究表明其不能棉线降低 AMS 发生率[50]。

急性高原反应是一种相对常见的情况，上升过快的人都会引起不同程度的不适症状。AMS 的临床过程通常是自限性和良性的，吸入氧气或下降可缓解不适症状。然而，如果不能下降或需进一步上升可能会加重病情，并可能导致更严重的不良反应、增加高原性脑水肿和高原性肺水肿的发生率。总而言之，逐渐上升，或者需在短时间内攀登，预防性使用乙酰唑胺可提高机体适应能力，减轻机体不良反应严重程度及降低机体不良反应发生率。

参考文献

[1] Simancas-Racines, D., Arevalo-Rodriguez, I., Osorio, D., Franco, J.V., Xu, Y. and Hidalgo, R. (2018) Interventions for Treating Acute High Altitude Illness. *Cochrane Database of Systematic Reviews*, **6**, Article ID: CD009567. https://doi.org/10.1002/14651858.CD009567.pub2

[2] Lee, E., Yim, S., Lee, S.K. and Park, H. (2002) Two Transactivation Domains of Hypoxia-Inducible Factor-1alpha Regulated by the MEK-1/p42/p44 MAPK Pathway. *Molecules and Cells*, **14**, 9-15.

[3] Dzhalilova, D. and Makarova, O. (2020) Differences in Tolerance to Hypoxia: Physiological, Biochemical, and Molecular-Biological Characteristics. *Biomedicines*, **8**, Article No. 428. https://doi.org/10.3390/biomedicines8100428

[4] Richalet, J.P., Larmignat, P., Poitrine, E., Letournel, M. and Canouï-Poitrine, F. (2012) Physiological Risk Factors for Severe High-Altitude Illness: A Prospective Cohort Study. *American Journal of Respiratory and Critical Care Medicine*, **185**, 192-198. https://doi.org/10.1164/rccm.201108-1396OC

[5] Schneider, M., Bernasch, D., Weymann, J., *et al*. (2002) Acute Mountain Sickness: Influence of Susceptibility, Preexposure, and Ascent Rate. *Medicine and Science in Sports and Exercise*, **34**, 1886-1891. https://doi.org/10.1097/00005768-200212000-00005

[6] Webb, J.D., Coleman, M.L. and Pugh, C.W. (2009) Hypoxia, Hypoxia-Inducible Factors (HIF), HIF Hydroxylases and Oxygen Sensing. *Cellular and Molecular Life Sciences*, **66**, 3539-3554. https://doi.org/10.1007/s00018-009-0147-7

[7] Minamino, T., Christou, H., Hsieh, C.M., Liu, Y., Dhawan, V., Abraham, N.G., Perrella, M.A., Mitsialis, S.A. and Kourembanas, S. (2001) Targeted Expression of Heme Oxygenase-1 Prevents the Pulmonary Inflammatory and Vascular Responses to Hypoxia. *Proceedings of the National Academy of Sciences of the United States of America*, **98**, 8798-803. https://doi.org/10.1073/pnas.161272598

[8] Agita, A. and Alsagaff, M.T. (2017) Inflammation, Immunity, and Hypertension. *Acta Medica Indonesiana*, **49**, 158-165.

[9] Maron, B.A., Kovacs, G., Vaidya, A., Bhatt, D.L., Nishimura, R.A., Mak, S., Guazzi, M. and Tedford, R.J. (2020) Cardiopulmonary Hemodynamics in Pulmonary Hypertension and Heart Failure: JACC Review Topic of the Week. *Journal of the American College of Cardiology*, **76**, 2671-2681. https://doi.org/10.1016/j.jacc.2020.10.007

[10] Villafuerte, F.C., Macarlupú, J.L., Anza-Ramírez, C., Corrales-Melgar, D., Vizcardo-Galindo, G., Corante, N. and León-Velarde, F. (2014) Decreased Plasma Soluble Erythropoietin Receptor in High-Altitude Excessive Erythrocytosis and Chronic Mountain Sickness. *Journal of Applied Physiology*, **117**, 1356-1362. https://doi.org/10.1152/japplphysiol.00619.2014

[11] West, J.B. (2011) Con: Headache Should Not Be a Required Symptom for the Diagnosis of Acute Mountain Sickness. *High Altitude Medicine & Biology*, **12**, 23-25. https://doi.org/10.1089/ham.2010.1068

[12] Marshall, J.M. (2015) Interactions between Local Dilator and Sympathetic Vasoconstrictor Influences in Skeletal Muscle In acute and Chronic Hypoxia. *Experimental Physiology*, **100**, 1400-1411. https://doi.org/10.1113/EP085139

[13] Bärtsch, P. and Bailey, D.M. (2014) Acute Mountain Sickness and High Altitude Cerebral Oedema. In: Swenson, E. and Bärtsch, P., Eds., *High Altitude*, Springer, New York, 379-404. https://doi.org/10.1007/978-1-4614-8772-2_20

[14] Davis, C. and Hackett, P. (2017) Advances in the Prevention and Treatment of High Altitude Illness. *Emergency Medicine Clinics*, **35**, 241-260. https://doi.org/10.1016/j.emc.2017.01.002

[15] Sampson, J.B., Cymerman, A., Burse, R.L., Maher, J.T. and Rock, P.B. (1983) Procedures for the Measurement of Acute Mountain Sickness. *Aviation, Space, and Environmental Medicine*, **54**, 1063-1073.

[16] Wilson, M.H., Newman, S. and Imray, C.H. (2009) The Cerebral Effects of Ascent to High Altitudes. *The Lancet Neurology*, **8**, 175-191. https://doi.org/10.1016/S1474-4422(09)70014-6

[17] Smedley, T. and Grocott, M.P. (2013) Acute High-Altitude Illness: A Clinically Orientated Review. *British Journal of Pain*, **7**, 85-94. https://doi.org/10.1177/2049463713489539

[18] Hall, D.P., Duncan, K. and Baillie, J.K. (2011) High Altitude Pulmonary Oedema. *BMJ Military Health*, **157**, 68-72. https://doi.org/10.1136/jramc-157-01-12

[19] Maggiorini, M. (2010) Prevention and Treatment of High-Altitude Pulmonary Edema. *Progress in Cardiovascular Diseases*, **52**, 500-506. https://doi.org/10.1016/j.pcad.2010.03.001

[20] Scherrer, U., Rexhaj, E., Jayet, P.Y., Allemann, Y. and Sartori, C. (2010) New Insights in the Pathogenesis of High-Altitude Pulmonary Edema. *Progress in Cardiovascular Diseases*, **52**, 485-492. https://doi.org/10.1016/j.pcad.2010.02.004

[21] Imray, C., Wright, A., Subudhi, A. and Roach, R. (2010) Acute Mountain Sickness: Pathophysiology, Prevention, and Treatment. *Progress in Cardiovascular Diseases*, **52**, 467-484. https://doi.org/10.1016/j.pcad.2010.02.003

[22] Wu, T., Ding, S., Liu, J., *et al*. (2006) Ataxia: An Early Indicator in High Altitude Cerebral Edema. *High Altitude Medicine & Biology*, **7**, 275-280. https://doi.org/10.1089/ham.2006.7.275

[23] Consolazio, C.F., Matoush, L.O., Johnson, H.L., *et al*. (1969) Effects of a High-Carbohydrate Diet on Performance and Clinical Symptomology after Rapid Ascent to High Altitude. *Federation Proceedings*, **28**, 937-943.

[24] Golja, P., Flander, P., Klemenc, M., Maver, J. and Princi, T. (2008) Carbohydrate Ingestion Improves Oxygen Delivery in Acute Hypoxia. *High Altitude Medicine & Biology*, **9**, 53-62. https://doi.org/10.1089/ham.2008.1021

[25] Lawless, N.P., Dillard, T.A., Torrington, K.G., Davis, H.Q. and Kamimori, G. (1999) Improvement in Hypoxemia at 4600 Meters of Simulated Altitude with Carbohydrate Ingestion. *Aviation*, *Space*, *and Environmental Medicine*, **70**, 874-878.

[26] Hackett, P.H. and Roach, R.C. (2001) High-Altitude Illness. *New England Journal of Medicine*, **345**, 107-114. https://doi.org/10.1056/NEJM200107123450206

[27] Pollard, A.J. (1992) Altitude Induced Illness. *British Medical Journal*, **304**, 1324-1325. https://doi.org/10.1136/bmj.304.6838.1324

[28] Ellsworth, A.J., Larson, E.B. and Strickland, D. (1987) A Randomized Trial of Dexamethasone and Acetazolamide for Acute Mountain Sickness Prophylaxis. *The American Journal of Medicine*, **83**, 1024-1030. https://doi.org/10.1016/0002-9343(87)90937-5

[29] Committee to Advise on Tropical Medicine and Travel (CATMAT) (2007) Statement on High-Altitude Illnesses. An Advisory Committee Statement (ACS). *Canada Communicable Disease Report*, **33**, 1-20.

[30] Nerín, M.A., Palop, J., Montaño, J.A., Morandeira, J.R. and Vázquez, M. (2006) Acute Mountain Sickness: Influence of Fluid Intake. *Wilderness & Environmental Medicine*, **17**, 215-220. https://doi.org/10.1580/1080-6032(2006)17[215:AMSIOF]2.0.CO;2

[31] Richardson, A., Watt, P. and Maxwell, N. (2009) Hydration and the Physiological Responses to Acute Normobaric Hypoxia. *Wilderness & Environmental Medicine*, **20**, 212-220. https://doi.org/10.1580/09-WEME-OR-272R1.1

[32] van Patot, M.C., Leadbetter 3rd., G., Keyes, L.E., *et al*. (2008) Prophylactic Low-Dose Acetazolamide Reduces the Incidence and Severity of Acute Mountain Sickness. *High Altitude Medicine & Biology*, **9**, 289-293. https://doi.org/10.1089/ham.2008.1029

[33] Basnyat, B., Gertsch, J.H., Johnson, E.W., *et al*. (2003) Efficacy of Low-Dose Acetazolamide (125 mg BID) for the Prophylaxis of Acute Mountain Sickness: A Prospective, Double-Blind, Randomized, Placebo-Controlled Trial. *High Altitude Medicine & Biology*, **4**, 45-52. https://doi.org/10.1089/152702903321488979

[34] Dumont, L., Mardirosoff, C. and Tramer, M. (2003) Efficacy and Harm of Pharmacological Prevention of Acute Mountain Sickness: Quantitative Systematic Review. *British Medical Journal*, **321**, 267-272. https://doi.org/10.1136/bmj.321.7256.267

[35] Basnyat, B., Gertsch, J.H., Holck, P.S., *et al*. (2006) Acetazolamide 125 mg BD Is Not Significantly Different from 375 mg BD in the Prevention of Acute Mountain Sickness: The Prophylactic Acetazolamide Dosage Comparison for Efficacy (PACE) Trial. *High Altitude Medicine & Biology*, **7**, 17-27. https://doi.org/10.1089/ham.2006.7.17

[36] Carlsten, C., Swenson, E.R. and Ruoss, S. (2004) A Dose-Response Study of Acetazolamide for Acute Mountain Sickness Prophylaxis in Vacationing Tourists at 12,000 Feet (3630 m). *High Altitude Medicine & Biology*, **5**, 33-39. https://doi.org/10.1089/152702904322963672

[37] Greene, M.K., Kerr, A.M., McIntosh, I.B. and Prescott, R.J. (1981) Acetazolamide in Prevention of Acute Mountain Sickness: A Double-Blind Controlled Cross-Over Study. *British Medical Journal*, **283**, 811-813. https://doi.org/10.1136/bmj.283.6295.811

[38] Her, Y., Kil, M.S., Park, J.H., Kim, C.W. and Kim, S.S. (2011) Stevens-Johnson Syndrome Induced by Acetazol-Amide. *The Journal of Dermatology*, **38**, 272-275. https://doi.org/10.1111/j.1346-8138.2010.00921.x

[39] Collier, D.J., Wolff, C.B., Hedges, A.-M., *et al*. (2016) Benzolamide Improves Oxygenation and Reduces Acute Mountain Sickness during a High-Altitude Trek and Has Fewer Side Effects than Acetazolamide at Sea Level. *Pharmacology Research & Perspectives*, **4**, e00203. https://doi.org/10.1002/prp2.203

[40] Ellsworth, A.J., Meyer, E.F. and Larson, E.B. (1991) Acetazolamide or Dexamethasone Use versus Placebo to Prevent Acute Mountain Sickness on Mount Rainier. *Western Journal of Medicine*, **154**, 289-293.

[41] Chen, G.-Z., Zheng, C.-R., Qin, J., *et al*. (2015) Inhaled Budesonide Prevents Acute Mountain Sickness in Young Chinese Men. *Journal of Emergency Medicine*, **48**, 197-206. https://doi.org/10.1016/j.jemermed.2014.07.047

[42] Zheng, C.-R., Chen, G.-Z., Yu, J., *et al*. (2014) Inhaled Budesonide and Oral Dexamethasone Prevent Acute Mountain Sickness. *The American Journal of Medicine*, **127**, 1001-1009. https://doi.org/10.1016/j.amjmed.2014.04.012

[43] Luks, A.M., McIntosh, S.E., Grissom, C.K., Auerbach, P.S., Rodway, G.W., Schoene, R.B., *et al*. (2010) Wilderness Medical Society Consensus Guidelines for the Prevention and Treatment of Acute Altitude Illness. *Wilderness & En-*

vironmental Medicine, **21**, 146-155. https://doi.org/10.1016/j.wem.2010.03.002

[44] Bartsch, P., Maggiorini, M., Ritter, M., Noti, C., Vock, P. and Oelz, O. (1991) Prevention of High-Altitude Pulmonary Edema by Nifedipine. *New England Journal of Medicine*, **325**, 1284-1289. https://doi.org/10.1056/NEJM199110313251805

[45] Sartori, C., Allemann, Y., Duplain, H., Lepori, M., Egli, M., Lipp, E., *et al*. (2002) Salmeterol for the Prevention of High-Altitude Pulmonary Edema. *New England Journal of Medicine*, **346**, 1631-1636. https://doi.org/10.1056/NEJMoa013183

[46] Maggiorini, M., Brunner-La Rocca, H.P., Peth, S., Fischler, M., Bohm, T., Bernheim, A., *et al*. (2006) Both Tadalafil and Dexamethasone May Reduce the Incidence of High-Altitude Pulmonary Edema: A Randomized Trial. *Annals of Internal Medicine*, **145**, 497-506. https://doi.org/10.7326/0003-4819-145-7-200610030-00007

[47] Luks, A.M., Auerbach, P.S., Freer, L., Grissom, C.K., Keyes, L.E., McIntosh, S.E., Rodway, G.W., Schoene, R.B., Zafren, K. and Hackett, P.H. (2019) Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. *Wilderness & Environmental Medicine*, **30**, S3-S18. https://doi.org/10.1016/j.wem.2019.04.006

[48] Gertsch, J.H., Corbett, B., Holck, P.S., Mulcahy, A., Watts, M., Stillwagon, N.T., *et al*. (2012) Altitude Sickness in Climbers and Efficacy of NSAIDs Trial (ASCENT): Randomized, Controlled Trial of Ibuprofen versus Placebo for Prevention of Altitude Illness. *Wilderness & Environmental Medicine*, **23**, 307-315. https://doi.org/10.1016/j.wem.2012.08.001

[49] Lipman, G.S., Kanaan, N.C., Holck, P.S., Constance, B.B. and Gertsch, J.H. (2012) Ibuprofen Prevents Altitude Illness: A Randomized Controlled Trial for Prevention of Altitude Illness with Nonsteroidal Anti-Inflammatories. *Annals of Emergency Medicine*, **59**, 484-490. https://doi.org/10.1016/j.annemergmed.2012.01.019

[50] Lundeberg, J., Feiner, J.R., Schober, A., Sall, J.W., Eilers, H. and Bickler, P.E. (2018) Increased Cytokines at High Altitude: Lack of Effect of Ibuprofen on Acute Mountain Sickness, Physiological Variables, or Cytokine Levels. *High Altitude Medicine & Biology*, **19**, 249-258. https://doi.org/10.1089/ham.2017.0144