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Hans汉斯

维生素D调控T细胞在儿童重症肺炎发病中的作用研究进展

郑艳兰，赵　峰

衡阳市妇幼保健院，湖南　衡阳

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摘　要

肺炎在发展中国家中是造成5岁以下儿童死亡和住院的最常见的原因，严重威胁儿童生命和健康。重症肺炎病情危重，进展迅速，易导致急性呼吸窘迫综合征、感染性休克、急性肾功能衰竭等并发症，对患者生命安全构成极大威胁。感染是儿童肺炎发生的最主要原因，病原体进入机体后，首先会激活固有免疫系统，当固有免疫无法清除入侵病原体时包括T细胞免疫在内的功能更强大的适应性免疫则会发挥效应。维生素D除了在骨稳态中的经典功能外，还在宿主防御、炎症、免疫和上皮修复发挥重要作用。维生素D缺乏的儿童在患重症肺炎时属于高危组，这意味着补充维生素D可能对这些患者有益。而T细胞在适应性免疫应答当中占据核心地位，维生素D可作为一种免疫调节剂通过直接、间接方式调控T细胞参与重症肺炎的发生、发展。本文综述维生素D调控T淋巴在细胞儿童重症肺炎发生发展中的作用及最新进展。

关键词

维生素D，T细胞，重症肺炎，感染，免疫

Research Progress on the Vitamin D in Regulating T Cells in the Pathogenesis of Severe Pneumonia in Children

Yanlan Zheng, Feng Zhao

Hengyang Maternal and Child Health Hospital, Hengyang Hunan

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Abstract

Pneumonia is the most common cause of death and hospitalization in children under 5 years of

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age in developing countries, posing a serious threat to children's lives and health. Severe pneumonia is severe and progresses rapidly, easily leading to acute respiratory distress syndrome, septic shock, acute renal failure and other complications, posing a great threat to patients' life safety. In addition to its classic function in bone homeostasis, vitamin D also plays an important role in host defense, inflammation, immunity, and epithelial repair. Children with vitamin D deficiency are in the high-risk group for severe pneumonia, meaning vitamin D supplements may benefit these patients. T cells play a central role in adaptive immune response, and vitamin D can directly and indirectly regulate T cells to participate in the occurrence and development of severe pneumonia as an immune modulator. This article reviews the role of vitamin D in regulating T lymphocytes in the development and progression of severe pneumonia in children.

Keywords

Vitamin D, T Cells, Severe Pneumonia, Infection, Immune

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1. 引言

维生素 D 以其在钙、磷和骨稳态中的作用而闻名，但近年来维生素 D 由于其广泛的骨外效应，包括免疫调节功能而受到广泛关注。T 淋巴细胞作为重要的免疫细胞在重症肺炎的发生、发展过程中发挥的巨大作用。在这篇综述中我们总结了目前关于维生素 D 作为免疫系统调节剂调控 T 细胞对儿童重症肺炎的影响机制，并对维生素 D 补充对于预防和治疗呼吸道感染作用进行探讨。

2. 儿童重症肺炎与肺脏－气道 T 细胞免疫

世界卫生组织将重症肺炎定义为以在肺炎基础上如果出现不能饮水、持续呕吐、抽搐、嗜睡或昏迷、小儿平静状态下的喘息或严重营养不良等肺外表现，则被称为重症肺炎[1]。依据病原学一般分为细菌、病毒、非典型病原体、真菌[2]和非感染性肺炎。儿童重症肺炎主要以感染性因素为主。

肺是免疫调节的主要部位，许多细胞如上皮细胞、树突状细胞、巨噬细胞、中性粒细胞、以及 B 和 T 淋巴细胞，均参与了肺部免疫[3]。感染性肺炎发生时首先启动的是固有免疫应答，当固有免疫应当无法清除入侵病原体时针对性更强、功能更强大的适应性免疫发挥作用。

T 淋巴细胞约占淋巴细胞在外周血总数的 60%，除了发挥细胞免疫功能外，B 细胞的活化、增殖、分化离不开 T 细胞的参与，最后其分泌的细胞因子亦可大幅度促进固有免疫应答，故 T 细胞在整个免疫系统中发挥了核心作用，具体见图 1。

当外界病原体突破气道上皮细胞屏障包括气道上皮的黏附分子组成的生理性屏障、纤毛系统、分泌系统(溶菌酶、乳铁蛋白、β-防御素)后，其表达的病原体相关模式分子(PAMP)可被气道上皮细胞表达 CD24、TLR1-TLR6、TLR9 识别，招募和激活中性粒细胞、巨噬细胞、DC 细胞等固有免疫细胞至感染部位，发挥固有免疫效应。随后活化的 DC 细胞、巨噬细胞均可作为抗原提呈细胞(APC)。APC 细胞与 MHC 分子结合，形成抗原肽-MHC 分子复合物，经 TCR 识别后诱导 T 细胞活化，分化为 CD4+T、CD8+T 功能亚群。一方面 CD4+T 识别抗原肽-MHC II 分子复合物生成辅助性 T 细胞(Th)，通过分泌 IFN-γ、TNF-α、IL-17、IL-2 等细胞因子活化中性粒细胞、巨噬细胞和 NK 细胞。另外活化 Th2 细胞表面 CD40L 与 B 细

胞表面 CD40 结合为 B 细胞活化提供了第二信号，并且 Th2 细胞通过分泌 IL-4、IL-5、IL-21 等细胞因子协助、促进 B 细胞分化为浆细胞从而产生抗体。另一方面 CD8+T 识别抗原肽-MHC I 分子复合物生成 CD8+T 细胞分化为细胞毒性 T 细胞(CTL)直接杀伤靶细胞。在这个过程中 IL-12、IFN-γ 诱导 CD4+T 向 Th1 分化，IL-4 诱导 CD4+T 向 Th2 分化，IL-6 诱导 CD4+T 向 Th17 分化。

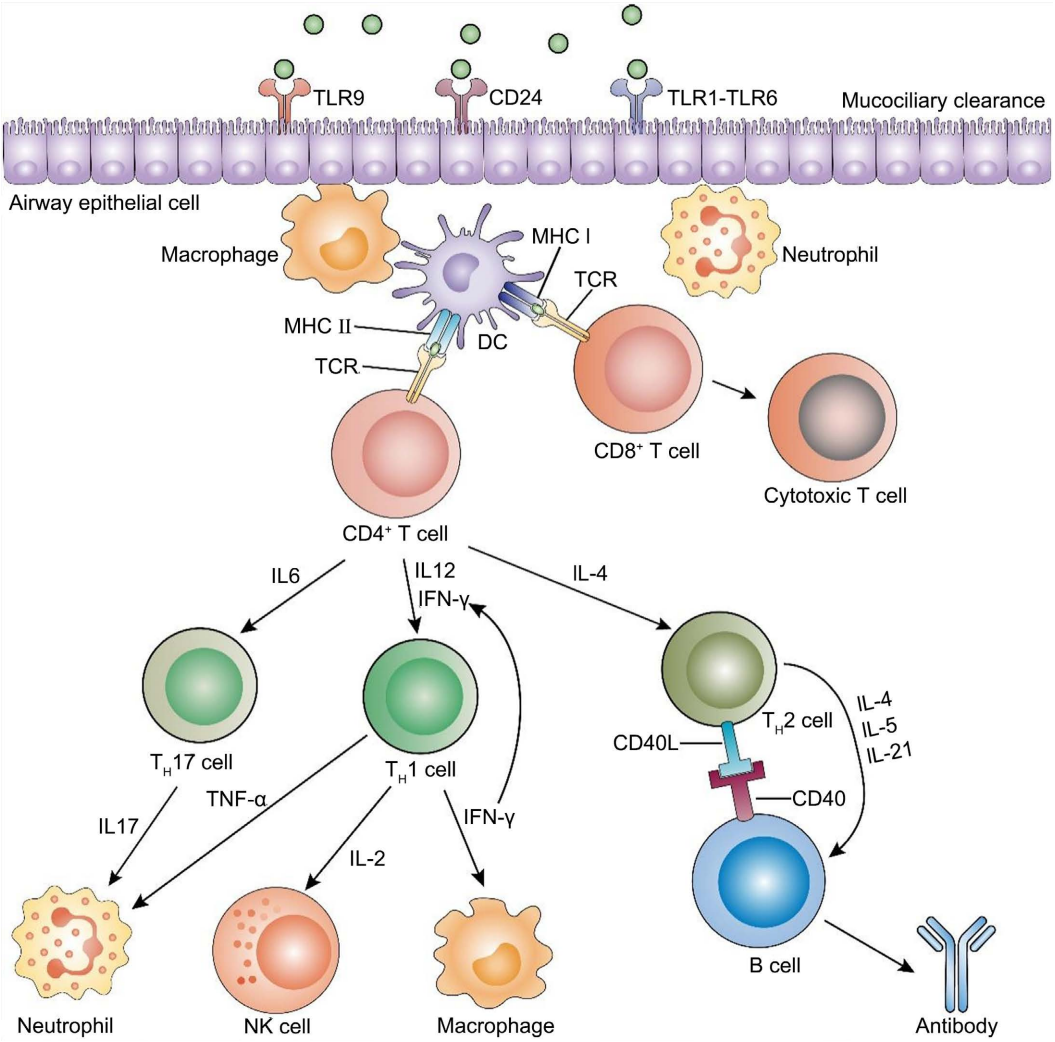

Figure 1. The mechanism of T cells in the entire immune system
图 1. T 细胞在整个免疫系统中作用机制

呼吸道不断暴露于外界环境，可作为许多病原体的主要入口。大多数情况下肺脏－气道的屏障功能及固有免疫系统可效地控制了多种肺部病原体，保护了宿主。然而，许多逃避这些先天防御的病原体需要上面提到的 T 细胞亚群来最终控制感染。CD4+T 细胞衰竭的艾滋病毒患者肺部感染的风险增加，包括耶氏肺孢子虫肺炎、肺结核、肺念珠菌病、组织胞浆菌病、复发性细菌性肺炎[4]、流感病毒、肺炎链球菌、流感嗜血杆菌[5]和烟曲霉菌[6]。有一项研究显示在机体免疫调节功能正常情况下 Th1 和 CD8+ T 细胞主要有助于宿主成功防御病毒病原体，如流感和 RSV，而 Th2 和 Th17 应答通常是有害的，并分别加剧了 RSV 和流感的疾病。Th1 和 Th17 细胞是抗细菌和真菌感染的重要组成部分[3]。另有一项研究显示，在感染性肺炎患者的 BAL 液中，IL-6、IL-8 和 IFN-γ 水平较健康者明显升高，且重症肺炎患者血清 IL-6、

IL-10 和 IFN-γ 水平显著高于非重症患者和健康人[7]。T 细胞的活化对建立细胞免疫和体液免疫至关重要，从而抑制呼吸道感染和预防严重疾病，而严重呼吸道感染中未解决的炎症反应与 T 细胞高且持续的活化相关[8] T 细胞应答的改变可能是急性呼吸窘迫综合征(ARDS)的部分原因[9] [10] [11]。可见重症肺炎的发生、发展全过程中离不开 T 细胞参与。

正常情况下机体在免疫调节作用下使免疫应答处在合适的强度和水平以维持机体内环境的稳定[12] [13]。其包括正向调节和负向调节，正向的主要为促进炎症反应，增强机体感染清除作用。负向的主要为抑制炎症反应，限制过度免疫反应对机体造成损伤。而在异常情况下机体促炎症因子和抗炎症因子平衡失调，大量的促炎细胞因子和趋化因子导致 T 细胞过度活化,T 下拨进一步释放细胞因子通过自分泌和旁分泌等级联反应进一步活化更多免疫细胞，造成免疫调控网络失衡，负反馈的缺失和正反馈的不断自我放大，形成细胞因子级联反应，导致细胞因子风暴的启动，损伤自身免疫系统稳态和正常组织细胞功能[14] [15] [16]，大量促炎症细胞因子释放导致肺泡上皮和肺毛细血管内皮通透性增加，促进富含蛋白质的血浆渗出，从而导致非心源性肺水肿、肺泡塌陷引发严重通气/血流比例失调，导致低氧血症、肺水肿、甚至 ALI/ARDS [17]。另外大量促炎症细胞因子释放引起全身性的毛细血管渗漏、血浆外渗、血液浓缩，亦可导致血管内皮细胞(ECs)功能障碍，使凝血与抗凝血平衡失调，导致循环衰竭和弥散性血管内凝血[18] [19]，严重者甚至危及生命。

3. 维生素 D 与重症肺炎

目前越来越多的证据支持维生素 D 缺乏与肺功能受损[20]、ALI/ARDS [21] [22]及炎症性疾病包括哮喘[23]、结核病[24]和慢性阻塞性肺疾病(COPD))之间存在关联[20] [25]。维生素 D 缺乏在肺炎危重患者中也很常见[21]。在重症肺炎或败血症患者中维生素 D 水平显著下调，并与预后相关[26] [27]。维生素 D 影响重症肺炎的可能机制为：1) 人气道上皮细胞同时表达 VDR 和 1a-羟化酶[28]。当肺炎发生时，肺内皮细胞将不活跃的维生素 D 转化为活性的 1,25-二羟基维生素 D[1,25(OH)2D]，并刺激抗菌肽的产生。抗菌肽的生产可直接杀灭多种微生物，包括革兰氏阳性和革兰氏阴性细菌、真菌和一些病毒，从而发挥其抗感染作用[29]。2) 维生素 D 缺乏可通过下调 Occludin 和 ZO-1 (zonula occludens-1)的表达，导致肺上皮屏障防御破坏，肺泡通透性增加，炎症细胞浸润，促炎细胞因子和趋化因子的释放，液体滞留。最终导致肺组织损伤和气体交换阻塞[30]。3) 维生素 D 通过直接调节人体的先天免疫和适应性免疫[31]，参与重症肺炎的发生和发展。

现有的研究结果显示体内低维生素 D 水平会增加呼吸道感染的发生率。一项 25-羟维生素 D(25-(OH)D)与成人 CAP 相关性的研究表明，当血清 25-(OH)D3 水平升高 10 nmol/L 时，呼吸道感染发生率降低 7% [32]。当血清 25-(OH)D3 < 37 nmol/L，CAP 住院可能性增加[33]。另有流行病学研究表明，维生素 d 水平与儿童呼吸道感染之间存在显著相关性，血清 VitD 低于 50 nmol/L 会使儿童患呼吸道感染的风险增加 70% [34]。同样，在健康成年人中，低于 30 ng/ml 的 25OHD 水平也与呼吸道感染风险增加相关[32] [35]。

但补充维生素 D 对于呼吸道感染的预防效果存在争议，并且目前的临床研究显示维生素 D 作为一种辅助治疗对于肺炎缓解并未取得令人满意的效果。有研究表明儿童补充维生素 D(3)可以降低甲型流感病毒、COVID-19 感染导致的呼吸道感染发病率[36] [37]。另一项研究显示幼儿单次口服大剂量补充维生素 D(3)并结合抗生素治疗，可减少肺炎重复发生概率[38]。但 Remmelt 等人的一项关于维生素 D 补充在肺炎发生中的作用的试验囊括了 33,726 例肺炎住院病人和 105,243 例对照组，分为 3 组进行对照研究，结果显示维生素 D 与肺炎发生风险之间的 OR 值分别为(1.716、1.028、1.65)，提示维生素 D 补充并不会降低甚至增加肺炎的发生率，但是当维生素 D 与糖皮质激素口服联合使用时 3 组 OR 值分别降为(0.826、0.854、0.817)，提示通过共同使用维生素 D 与糖皮质激素显著改变了这种相关性，似乎降低了肺炎的发

生率[39]。在治疗效果方面有研究认为在抗生素治疗的同时补充维生素 D 对肺炎缓解并没有明显的益处[38] [40]。

造成这些结果的原因可能是多方面的，包括：1、激素抗炎作用强于 VD，特别是在重症肺炎生发时，单纯 VD 的抗炎效应不足以及时有效清除炎症风暴，相反激素具有强大的抗炎作用，能保护宿主免受过量炎症因子释放所造成伤害。2、VD 与糖皮质激素之间的协同作用，有研究显示 VD 与糖皮质激素之间具有协同作用，VD 能增强糖皮质激素抗炎作用并逆转激素抵抗[41]。3、实验设计相关因素，VD 作为肺炎的辅助治疗其效果可能受多方面因素影响，包括受试者的基础维生素 D 水平、维生素 D 服用剂量、服用时间甚至不同的肺炎病原学等。当这些因素未设置统一标准时均可对实验结果产生重大影响。

4. 维生素 D 代谢与生物功能

维生素 D 是一种类固醇激素，在紫外线照射下在皮肤中由 7-脱氢胆固醇转化为维生素 D 原，并异构化为维生素 D [42]。少量的维生素 D 也可以通过饮食获得，包括鱼肝油和脂肪多的鱼；紫外线照射过的蘑菇;含有维生素 D 和补充剂的强化食品[43] [44]。维生素 D 必须通过至少 5 种酶(即 CYP2DII、CYP2D25、CYP3A4、CYP2R1 和 CYP27A1)发生 25-羟基化[45]，形成 25 羟基维生素 D [25(OH)D]。随后 25(OH) D 必须在肾脏或体外通过 1α 羟化酶(CYP27B1)进行第二步羟化，形成具有生物活性的 1,25(OH)2D3 [46]。

1,25(OH)2D3 通过和高亲和维生素 D 受体(VDR)结合调控基因转录来实现其许多生物学功能。VDR 分为细胞膜受体和核受体。细胞膜受体途径又称非核受体途径，主要调节钙和磷的代谢。核受体途径调控基因转录[47] [48]。在核受体途径中，1,25(OH)2D3 作为配体与核内的 nVDR 和 RXR 结合，形成 VDR 与视黄酸 X 受体(RXR)的异源二聚体。VDR RXR 异源二聚体特异性结合 DNA 靶基因的启动子结构域，调控靶基因转录蛋白合成，发挥生物学作用[49]。

人体约有 2000 个基因直接或间接地受到维生素 D 的调控，表明维生素 D 具有广泛的生物学作用[49]。有研究表明 1,25(OH)2D3 作为一种免疫调节剂靶向各种免疫细胞，包括单核细胞、巨噬细胞、树突状细胞(DCs)以及 T 淋巴细胞和 B 淋巴细胞，因此可以调节先天和适应性免疫反应[31]。这提示了维生素 D 可能通过免疫调节作用影响重症肺炎的发生、发展。

5. 维生素 D 调控 T 细胞影响重症肺炎

维生素 D 对 T 细胞的影响包括间接影响和直接影响，间接影响主要表现在以下 2 个方面：1) 1,25-(OH)2D3 降低 DCs 细胞、单核细胞/巨噬细胞的抗原提呈作用和共同刺激因子，导致 T 细胞的增值和分化不良，使 T 细胞免疫效应下降[50] [51] [52] [53]。2) 维生素 D 处理可明显减弱 toll 样受体 4 (TLR4)的表达，从固有免疫方面而发挥其抗炎、抗凋亡功能[54] [55]。另 APC 表面 TLR 与病原体相关模式分子(PAMP)结合后激活，可表达多种共同刺激分子和细胞因子，从而介导 T 细胞激活和增值[56]。当维生素 D 减弱 toll 样受体 4 (TLR4)的表达后可能通过此途径间接影响 T 细胞免疫。

5.1. 维生素 D 和 Th1、Th17

维生素 D 对 T 细胞的直接影响主要表现在：1,25-(OH)2D3 抑制 Th1 细胞 IL-2、IFN-γ 的分泌[57] [58] [59]。IL-2 作为促炎症因子，能促进 T 细胞亚群增值及产生细胞因子，另可以促进 NK 细胞毒活性及产生细胞因子，另可活化 B 细胞增殖及产生抗体，还可激活巨噬细胞增强其杀灭病原体能力。IFN-γ 是激活单核巨噬细胞的关键因子，可促进 Th0 细胞分化为 Th1 细胞，在体外和人体试验中显示 IFN-γ 对于细菌性肺炎[60] [61]、流感病毒感染[62] [63]及 RSV 肺炎[64] [65]、肺部真菌感染[66] [67] [68]均产生有益影响。

1,25(OH) 2d 也被证明能抑制 Th17 细胞分泌 IL-17 [69] [70]。IL-17 的主要功能是通过诱导中性粒细

胞为主的炎症反应，吞噬和杀伤病原体，一项与肺炎有关的相关实验表明：CAP 患者血液及 BAL 中 IL-17A 阳性 CD4 T 细胞较健康者明显增加[71]。另外与病原学相关的体外试验显示 IL-17 对机体的肺炎克雷伯菌感染[72] [73]、支原体感染[74]、肺炎链球菌感染[75]和铜绿假单胞菌感染[76]产生保护效果，但在流感亚型 PR8 感染中对宿主有害[77]，另外真菌病原体诱导的 Th17 应答对宿主既可能是保护性的，也可能是有害的[78] [79]。

在机体免疫调控功能正常情况下，大多数情况维生素 D 对 Th1 和 Th17 在肺炎中的调控是有益于机体的，但这种有益影响可能出现改变，重症肺炎发生时，机体免疫平衡失调，过多的促炎症因子释放(包括 IL-2、IFN-γ、IL-17)可能导致这种有益影响转变成有害的，而维生素 D 作为免疫调节剂通过抑制 IL-2 和 IFN-γ、IL-17 的分泌控制炎症反应，避免组织过度的损伤。

5.2. 维生素 D 和 Th2

Th2 主要通过辅助活化 B 细胞发挥免疫共功能，另可参与超敏反应的发生和抗寄生虫感染。1,25(OH)2D3 对 Th2 细胞因子的影响存在争议。有研究表明，1,25(OH)2D3 可上调 Th2 特异性转录因子 GATA-binding protein 3 (GATA-3)和 c-maf 的水平，以及诱导 IL-4、IL-5 等 Th2 细胞因子，但也有研究成相反观点[70] [80] [81] [82]。相关试验表明肺部 Th2 反应在宿主防御寄生虫[83]、流感病毒[84] [85] [86] [87]、真菌感染[88]方面发挥了有益的作用。但由于维生素 D 对于 Th2 细胞影响尚无定论，故维生素 D 对 Th2 在重症肺炎中的调控对于人体是否获益有待进一步的研究。

5.3. 维生素 D 和 CD8+T 细胞

CD8+T 细胞在外周免疫器官活化、增殖、分化为效应 CTL 细胞，可高效、特异性的杀伤细胞内寄生病原体，也可通过产生 IFN-γ、TNF-α、IL-2 调节免疫应答。体外试验显示:在肺部细菌性感染[89] [90]、肺部真菌感染[91] [92]、流感病毒感染[93]时 CD8+ T 细胞介导的免疫反应对机体起保护作用，但有时也能造成组织损伤[94] [95]，造成这种结果的原因可能类似于 Th1 介导的免疫损伤机制。当重症肺炎发生时免疫调节失衡，而 TNF-α 和 IFN-γ 作为主要的促炎症因子过度释放会导致肺部的病理损伤[94]，而 1,25(OH)2D3 可通过抑制 CD8 T 细胞中 IFN-γ、TNF-a [96]和 IL-2 [97]的产生抑制过度的炎症反应从而在重症肺炎中发挥保护作用。

6. 总结

目前大量的实验研究表明，维生素 D 作为免疫调节剂在体外和动物模型中对于机体感染性肺炎的影响是正面的。现有的数据支持维生素 D 通过调控 T 细胞过度的炎症反应、诱导免疫耐受降低机体在重症肺炎的免疫损伤。但维生素 D 的补充预防或改善治疗呼吸道感染的临床试验结果不一致，差异的原因可能是混合因素：如在小样本量的干预研究，参与者在种族、年龄、体重指数(BMI)、季节、日照、药物剂量等方面差异很大。另外这些研究缺乏对患者维生素 D 水平的评价。重症肺炎治疗前是否应先完善维生素 D 水平测定？在严重肺炎的情况下，维生素 D 作为辅助治疗是否确实对缺乏维生素 D 的患者有益，但对没有缺乏维生素 D 的患者无效甚至加重？最后从目前的研究可得出维生素 D 补充在呼吸道感染中的效果受不同病原体差异的影响，如在部分病原体感染中可能使患者收益，另一部分可能有害，评估效果应根据不同病原学做区分。后续应采用双盲、大样本研究，需更严谨的试验设计，随访时间需更长、更严格、更规范，为临床提供了理论依据，为重症肺炎的辅助治疗开辟了新的途径。

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