

doi: 10.13241/j.cnki.pmb.2022.01.008

通络益气方对博来霉素致大鼠肺纤维化的治疗作用研究*

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摘要 目的:研究通络益气方对博来霉素致大鼠模型肺组织病理及肺组织羟脯氨酸(HYP)的影响。**方法:**将 36 只 SPF 级健康 6 周龄 Wistar 雄性大鼠置于 SPF 级条件下,适应性试养 3 天后,分为 3 组:空白组、模型组、治疗组,每组 12 只。除空白组外,其余两组,在清醒状态下,放入与小动物雾化给药仪相连的 30 cm×30 cm×20 cm 自制玻璃箱中,雾化吸入浓度为 5 g/L(50%)的博来霉素,雾化 20 分钟,休息 5 分钟,一天连续激发 2 小时,连续刺激 4 周。空白组在同样条件下雾化吸入 0.9%生理盐水,操作方法与其余两组相同。治疗组大鼠造模后第 2 天起给予通络益气方,通络益气方溶液按体质量给予大鼠药液 1 mL/100 g 灌胃,每次于雾化前 1 h 灌胃;模型组、正常组均给予生理盐水(1 mL/100 g)灌胃。各组大鼠连续刺激 4 周后,用 1%戊巴比妥钠(50 mg/kg)麻醉后,待其肌肉松弛、呼吸平稳后,仰面固定于专用板上,用动物专用 CT 进行肺扫描。各组大鼠在末次诱导后,24 h 内腹腔注射 1%戊巴比妥钠麻醉后,取肺组织进行 HE 和 Masson 染色,观察各组大鼠肺组织病理 HE 染色、Masson 染色及肺组织中 HYP 的含量。**结果:**与空白组(0.76±0.06)相比,治疗组(1.11±0.13)、模型组(1.47±0.22)HYP 均升高($P<0.05$);与模型组(1.47±0.22)相比,治疗组(1.11±0.13)HYP 明显降低($P<0.05$)。**结论:**通络益气方能降低对肺纤维化大鼠肺组织中胶原的沉积,起到治疗肺纤维化的作用,与通络益气方抑制 HYP 胶原蛋白的表达有关。

关键词:通络益气方;中医药;动物模型;肺纤维化;羟脯氨酸

中图分类号:R-33;R563;R256 **文献标识码:**A **文章编号:**1673-6273(2022)01-52-05

Studies on Therapeutic Effect of Tongluo Yiqi Recipe on Bleomycin-induced Pulmonary Fibrosis in Rats*

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ABSTRACT Objective: To study the effect of Tongluo Yiqi Recipe on lung tissue pathology and lung tissue hydroxyproline (HYP) in a rat model induced by bleomycin. **Method (s):** 36 SPF-grade healthy 6-week-old Wistar male rats were placed under SPF-grade conditions. After 3 days of adaptive trial rearing, they were divided into 3 groups: blank group, model group, and treatment group, with 12 rats in each group. Except for the blank group, the other two groups were awake and placed in a 30 cm×30 cm×20 cm self-made glass box connected to the small animal nebulization dosing device. The inhalation concentration was 5 g/L (50%). Lymycin, sprayed for 20 minutes, rested for 5 minutes, stimulated continuously for 2 hours a day, stimulated continuously for 4 weeks. The blank group inhaled 0.9% saline under the same conditions, and the operation method was the same as that of the other two groups. The rats in the treatment group were given Tongluo Yiqi Recipe from the 2nd day after modeling, and the Tongluo Yiqi Recipe solution was given to the rats by gavage of 1 mL/100 g of liquid medicine according to their body weight, each time 1 hour before nebulization; Both the model group and the normal group were given saline (1 mL/100 g) by gavage. After 4 weeks of continuous stimulation, rats in each group were anesthetized with 1% sodium pentobarbital (50 mg/kg), and after their muscles were relaxed and breathing was stable, they were fixed on their backs on a special board, and the lungs were scanned by animal CT. After the last induction, rats in each group were anesthetized by intraperitoneal injection of 1% sodium pentobarbital within 24 hours, and then lung tissues were taken for HE and Masson staining to observe the pathological HE staining, Masson staining and the content of HYP in the lung tissues of rats in each group. **Results:** Compared with the blank group, the HYP of the treatment group and the model group were increased ($P<0.05$); compared with the model group, the HYP of the treatment group was significantly lower ($P<0.05$). **Conclusion (s):** Tongluo Yiqi Decoction can reduce the deposition of collagen in lung tissues of pulmonary fibrosis rats, and play a role in treating pulmonary fibrosis, which is related to the inhibition of HYP collagen expression by Tongluo Yiqi Decoction.

Key words: Tongluo Yiqi Recipe; Chinese medicine; Animal model; Pulmonary Fibrosis; Hydroxyproline

Chinese Library Classification(CLC): R-33; R563; R256 **Document code:** A

Article ID: 1673-6273(2022)01-52-05

* 基金项目:黑龙江省自然科学基金重点项目(ZD2018019);黑龙江省博士后面上资助项目(LBH-Z19100)

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(收稿日期:2021-04-27 接受日期:2021-05-23)

前言

肺纤维化是目前呼吸系统的疑难疾病,发病机制还没有完全阐明,其高损伤性、进行性、不可逆性的临床特征和逐年上升的发病率与死亡率^[1],给临床治疗带来了很大难度^[2,3],其发病与肺泡上皮细胞的反复损伤^[4]、应激^[5]、凋亡^[6],成纤维细胞上皮-间充质转化激活^[7],肌成纤维细胞的活化和积累^[8],以及肺泡上皮细胞不能进行正常的修复重建有关^[9]。虽然新型抗纤维化药物^[10,11](吡非尼酮和尼达尼布)可减缓患者用力肺活量的下降,但无法控制肺纤维化的进展,也无法使肺纤维化逆转,长期服用会出现很多不良反应,且维持剂量不易把控,长时间应用难度较大^[12]。多年的临床表明中药复方在抑制肺泡间质纤维化的进程、阻止肺泡间质纤维化的致肺纤维化病变、调节免疫功能、改善肺循环、抗炎、抑制肺血管重塑^[13,14]等方面具有良好的前景。课题组临床中已掌握了该病的证候演变规律和辨证论治的特色方案,通过从炎症因子、血管新生及胶原蛋白和细胞代谢等层面探讨中医药抗肺纤维化的作用机制^[15],证实中医药能多途径、多环节、多靶点相互伍用干预肺纤维化^[16]。从多角度、多层次、多因素研究肺纤维化的细胞凋亡是国内外医学研究热点,而国内关于中药对肺纤维化影响的研究大多局限于相关因子的研究,从多种相关因子及其相互作用的层面上阐述中药干预细胞凋亡的机制的研究较少。为进一步研究评估中医药在改善肺纤维化和抗纤维化方面的具体靶点和作用机制,研究表明,临床需要更加贴近病理改变的动物模型^[17],如何复制有效的肺纤维化动物模型,对临床研究和治疗肺纤维化都具有重要意义。为使动物模型肺部病理形态更接近于人体肺纤维化的慢性弥漫性改变的特点,本文应用博来霉素(Bleomycin, BLM)雾化吸入给药的方式诱导 Wistar 大鼠肺纤维化造模。

1 材料与方法

1.1 材料

健康 6 周龄 Wistar 雄性大鼠 36 只(SCXK(黑)2019-002),体质量(200±20)g,由黑龙江中医药大学实验动物中心提供。实验室温度 18~25℃,相对湿度 40%~75%。博来霉素(国药准字 H20055883,瀚晖制药有限公司);Masson 染色试剂盒(南京森贝伽生物科技有限公司);羟脯氨酸(Hyp)测定试剂盒(南京建成生物有限公司);电子精密天平;METTLER TOLEDO;光学显微镜;OLYMPUS;小动物雾化给药仪:赛昂斯;自制玻璃雾化箱;自制 30 cm×30 cm×20 cm。

1.2 方法

1.2.1 中药制剂制备 通络益气方:黄芪 30 g、党参 20 g、麦冬 15 g、五味子 15 g、丹参 15 g、桃仁 15 g、川芎 15 g、水蛭 5 g、桔梗 15 g、浙贝母 10 g。将以上 10 味中药,按照常规比例加清水浸泡一小时,煎煮一小时,滤出煎煮液,再加清水后直接煎煮,再次滤出煎煮液,将两次煎煮液合并后进行浓缩,浓缩成浸膏(相对密度 1.15~1.20),真空干燥后制成颗粒备用,其含量约为每 1 kg 含 81 g 生药,使用前加水稀释,根据人(70 kg)与大鼠(200 g)给药剂量比值 1:0.018 换算后,给予大鼠药液 1 mL/100 g 灌胃。

1.2.2 实验分组 参照文献 [18] 将 SPF 级 Wistar 大鼠置于

SPF 级条件下,先适应性试养 3 天。每次将 5 只清醒的大鼠放入与小动物雾化给药仪相连的 30 cm×30 cm×20 cm 自制玻璃箱中,雾化吸入浓度为 5 g/L(50%)的博来霉素,雾化 20 分钟,休息 5 分钟,一天连续激发 2 小时,连续刺激 4 周。将 36 只大鼠分为 3 组,分别为:空白组、模型组、治疗组,每组 12 只。治疗组大鼠造模后第 2 天起给予通络益气方,通络益气方溶液按体质量给予大鼠药液 1 mL/100 g 灌胃,每次于雾化前 1 h 灌胃;模型组、正常组均给予生理盐水(1 mL/100 g)灌胃。

1.2.3 一般情况观察 将实验各组大鼠放入与雾化器相联的透明有机玻璃盒中,采用博来霉素稀释液进行激发,每次激发 20 分钟,连续激发 2 小时并进行一般状态记录。

1.2.4 观察各组大鼠影像学情况 各组大鼠连续刺激 4 周后,用 1%戊巴比妥钠(50 mg/kg)麻醉后,待其肌肉松弛、呼吸平稳后,仰面固定于专用板上,防止大鼠活动影响扫描结果,于动物专用 CT 进行肺扫描。

1.2.5 肺组织病理取材 各组大鼠在末次诱导后,24 h 内腹腔注射 1%戊巴比妥钠麻醉,麻醉完全后,清洁胸腔区域,逐层打开,让肺组织充分暴露,分离周围组织,取左肺组织置于 4%多聚甲醛中固定,取右肺组织用铝箔包裹,液氮冻存,取材结束后转移到 -80℃冰箱中保存。

1.2.6 HE 染色 将 4%多聚甲醛固定的左肺组织取出,严格按照 HE 染色操作,先进行脱水,再石蜡包埋,然后切片、染色。肺泡炎和肺纤维化的评定照 SV Szapiel^[19]等方法进行。

1.2.7 Masson 染色 在光镜下观察肺壁微量纤细的胶原纤维,是目前应用最为广泛、最直观的观察方法之一。按照 Masson 染色的操作要求,将石蜡包埋的大鼠肺组织,脱蜡、染色、再次脱水、透明、封片逐步有序进行。本实验中阳性结果为肺组织内胶原纤维沉积呈现绿色表达。

1.2.8 肺组织中羟脯氨酸的测定 研究发现胶原蛋白中含有一种特殊的氨基酸--羟脯氨酸,羟脯氨酸的含量高低,常被作为衡量胶原蛋白含量的指标,也可间接评定纤维化病变程度^[20,21]。

按照说明操作测定,氯胺 T 氧化游离的羟脯氨酸后,生成的吡咯与对二甲胺基苯甲醛(P-DMAB)P-DMAB 结合,发生反应,形成红色的化合物,在波长 550 nm 处测定其吸光度,并进行记录。

1.3 统计学分析

采用 SPSS19.0 统计软件进行统计,计量的指标采用 $\bar{x} \pm s$ 表示, $P < 0.05$ 且具有统计学意义。

2 结果

2.1 一般状态情况变化

空白组:毛发光亮,反应敏捷,进食及饮水良好,喜动好斗,体重增加匀速。模型组:倦态懒动,呼吸频率加快,口唇发绀,甚至有喘促征象,容易烦躁,肢体活动明显减少,弓背蜷缩,食欲减退,体重较造模之前明显减轻,毛色稀疏枯槁而失去光泽时有脱落,上述症状的出现随造模时间延长而加重。治疗组:在造模早期大鼠状态与模型组相当,随着通络益气方的干预,喘促症状缓解,逐渐喜动好斗,毛发逐渐恢复光亮,反应速度增快,食量、饮水较造模初期明显增加,少数出现倦卧、呼吸增快。

2.2 肺部 CT 扫描

空白组扫描结果显示,双肺支气管走行光滑规则、血管分布均匀,胸膜未见增厚,肺纹理清晰,无占位等异常。模型组双

肺支气管走行紊乱,局部有纤维条索网格样改变及肺大泡,胸膜肥厚,局限性毛玻璃样改变。治疗组双肺支气管走行相对紊乱,有少量出现磨玻璃结节影及网格状改变。见图 1。

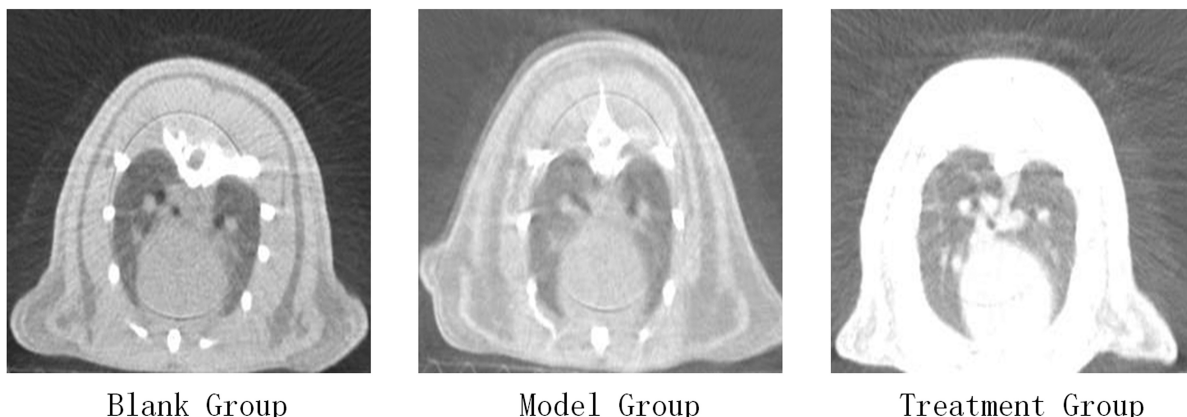


图 1 各组大鼠肺 CT 改变的比较

Fig.1 Comparison of CT changes in the lungs of rats among different groups

2.3 各组大鼠肺组织外观观察

空白组肺组织光滑、有弹性,色泽粉红,整体润泽。模型组:肺组织明显缩小,局部突起或萎缩,表面不光滑,色泽暗,散在瘀点,整体颜色苍白,弹性减小。治疗组:肺组织较空白组体积略小,局部突起或萎缩减少,色泽略暗,瘀点较模型组明显减少,弹性较模型组改善。

空白组大鼠支气管及肺泡结构完整,肺泡壁、肺泡腔分布均匀,组织内未见浸润炎症细胞及胶原沉积表现。模型组大鼠肺组织中,无完整肺泡结构,被炎性细胞破坏浸润,间质内可见广泛纤维瘢痕。治疗组大鼠肺组织中,肺泡结构欠规整,间质纤维胶原沉积减轻,肺泡壁增厚,局部浸润少许炎性细胞。见图 2。

2.4 各组大鼠肺组织 HE 结果

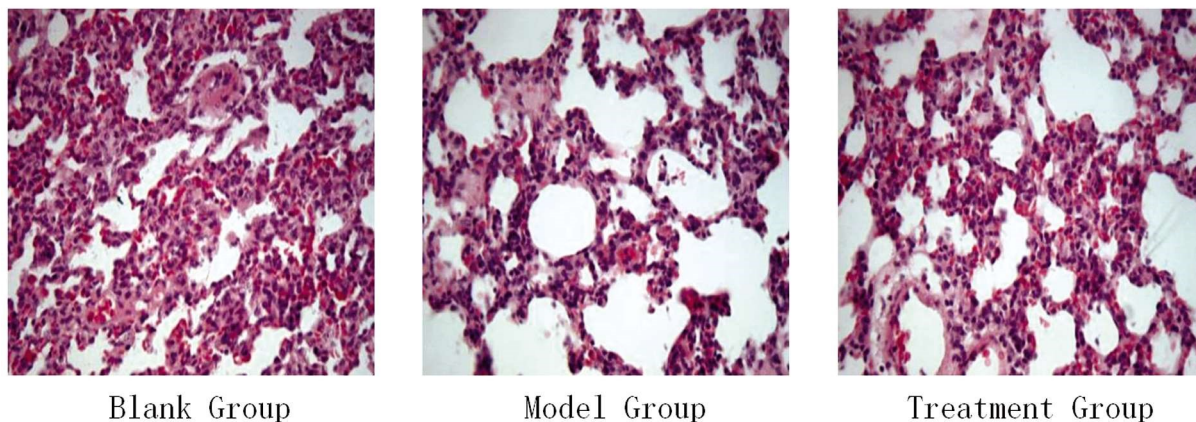


图 2 各组大鼠肺组织 HE 结果的比较($\times 400$)

Fig.2 Comparison of HE results in lung tissues of rats among different groups

2.5 各组大鼠肺组织 Masson 结果

空白组大鼠肺泡结构完整,周围可见极少数淡绿色胶原沉积。模型组肺泡结构不完整,支气管壁、血管壁周围可见大量绿色胶原沉积,呈现出弥漫性的中重度肺纤维化表现。治疗组肺泡结构欠完整,周围可见少量淡绿色胶原沉积。见图 3。

2.6 各组大鼠肺组织羟脯氨酸测定

肺组织在炎症因子和各种活性物质的刺激下,分泌产物增多,尤其是纤维母细胞在不断的刺激下,分泌出大量胶原蛋白,促进了肺间质纤维化的胶原沉积,因此羟脯氨酸的含量高低可以作为肺纤维化病变的指标。治疗组与模型组和空白组比较差异都有统计学意义($t=17.631, t=18.226, P<0.05$)。见表 1。

3 讨论

在中医理论中通常将肺纤维化归属为“喘证”“肺痿”“肺痹”等症范畴。结合近代医家对该病的认识^[22,23],纵观肺纤维化发病的中医病理过程,早期多因风、寒、痰、湿、热等邪气痹阻有关,引起后期肺、脾、肾三脏痿弱无力,病程中虚实夹杂、痹痿并行。课题组经过多年临床实践并总结历代医家的经验,发现间质性肺疾病(ILD)从临床表现上与肺痹更为相似。通络益气方具有活血化痰通络、益气养阴,促进各脏腑功能的恢复,该方在临床中运用多年,对控制及改善肺纤维化患者临床症状及肺功等方面有较好疗效^[24]。既往的研究发现,通络益气方具有相似

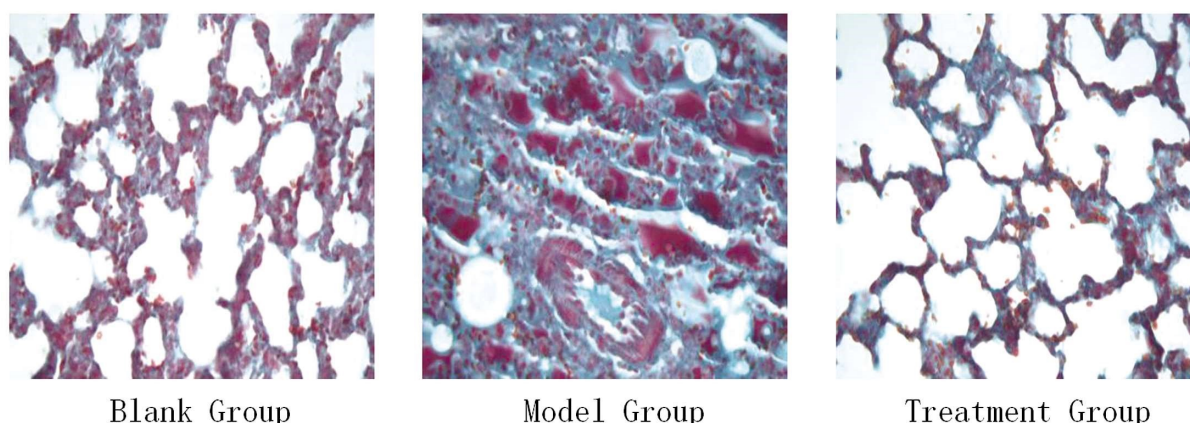
图3 各组大鼠肺组织 Masson 结果的比较($\times 400$)

Fig.3 Comparison of Masson results in lung tissues of rats among different groups

表1 三组大鼠肺组织羟脯氨酸测定情况($\bar{x} \pm s$)Table 1 Determination of hydroxyproline in lung tissues of three groups of rats($\bar{x} \pm s$)

Groups	Amount(n)	Determination of hydroxyproline(mg/g)
Treatment Group	10	$1.11 \pm 0.13^* \blacktriangle$
Blank Group	12	$0.76 \pm 0.06^*$
Model Group	9	$1.47 \pm 0.22^\blacktriangle$

Note: compared with the Model Group, * $t=17.631$; compared with the Blank Group, $\blacktriangle t=18.226$, $P<0.05$.

强的松的抗纤维化作用,可抑制血清中的 $\text{TNF-}\alpha$ 的表达及促进 $\text{INF-}\gamma$ 的分泌,进而改善肺纤维化大鼠的病理进程^[13,14],其具体作用机制还有待进一步研究,但为肺纤维化的治疗提供了新的选择方向。

通络益气方中黄芪归肺、脾经,补气固表,党参归脾、肺经,补中益气,健脾益肺,黄芪与党参相合共为君药,补中气,补脾肺之气;麦冬归心、肺、胃经,能养阴生津,润肺清肺,降肺热,保肺气。五味子归肺、心、肾经,收敛固涩,益气生津,补肾宁心,用于喘咳燥嗽,具有壮水镇阳之功。麦冬、五味子相伍助参芪益气养阴,为臣药;丹参祛瘀止痛,活血通经,桃仁活血祛瘀,止咳逆上气,通脉,止痛。川芎活血行气,祛风止痛,上行头目,下调经水,中开郁结,血中气药。水蛭破血、逐瘀、通经、破坚积、攻积滞,四药活血通络共为佐药;桔梗归肺经,宣肺、祛痰,用于咳嗽痰多,胸闷不畅,浙贝母归肺、心经,开宣肺气,清热解毒散结,利痰止咳,桔梗、浙贝母二药相伍清热宣肺化痰散结,共为使药。诸药共奏益气养阴活血通络之功。

对通络益气方的网络药理学^[15]分析得到核心靶点蛋白为花生四烯酸 5-脂氧合酶(Arachidonate 5-lipoxygenase),而在药理学研究中提示花生四烯酸 5-脂氧合酶在抑制大鼠肝脏纤维化形成方面起到良好作用^[25]。本方中的丹参所含氨基琥珀酸(2-Aminosuccinic acid)、党参所含辣椒素(辣椒素)和 2,3-二羟丁二酸(2,3-Dihydroxybutanedioic acid)、五味子所含原儿茶酸(Protocatechuic acid)、黄芪所含芦丁(Rutin)、山奈酚(Kaempferol)、香豆素(Coumarin)和槲皮素(Quercetin)等成分均对肺纤维化的核心靶点花生四烯酸 5-脂氧合酶有直接作用关系^[15]。本文采用大鼠雾化博来霉素方法,模拟制备具有肺纤维化病理特点的动物模型,并通过通络益气方益气养阴活血通络之功干预其肺纤维化的发展,改善大鼠肺纤维化的程度,研

究结果证实,通络益气方可以抑制肺纤维化大鼠的肺泡炎^[26],降低肺组织中间质性胶原蛋白的沉积^[27,28]。前期的临床研究证实中药可以延缓肺纤维化患者的进展,改善生存质量,干预其肺功能的下降,我们推测通络益气方可以降解细胞外胶原蛋白,减少成纤维细胞的异常积聚,其作用途径可能是通络益气方减少细胞外基质的增殖。研究结果也证实通络益气方可以明显降低羟脯氨酸含量,与模型组比较,具有统计学意义,这与相关的报道结果是相吻合的^[29,30]。

本研究通过观察各组肺纤维化大鼠一般情况、大鼠肺病理情况以及肺组织 HYP 含量变化,表明通络益气方可抑制 HYP 胶原蛋白的表达,从而干预肺纤维化大鼠病理改变。我们的研究表明中医药在间质性肺疾病方面具有明显的干预和治疗作用,值得进一步深入探讨研究。

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