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支气管肺发育不良与解脲脲原体的关系的研究进展

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摘　要

支气管肺发育不良(bronchopulmonary dysplasia, BPD)是一种以肺泡简单化、肺微血管发育障碍，伴随肺间质纤维化、肺不张及囊性变为病理特征的早产儿常见慢性肺部疾病。随着早产儿存活率的提高，BPD发生率也有逐年上升的趋势，BPD可导致慢性心肺及神经系统后遗症，严重影响早产儿的存活率及远期生存质量，成为NICU最为棘手的问题之一。近年来越来越多的文献报道解脲脲原体(*Ureaplasma urealyticum*, UU)的感染与BPD的发生发展有关，本文就支气管肺发育不良与解脲脲原体的关系的研究进展进行综述。

关键词

支气管肺发育不良，解脲脲原体，炎症反应，阿奇霉素

Research Progress on the Relationship between Bronchopulmonary Dysplasia and *Ureaplasma urealyticum*

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Abstract

Bronchopulmonary dysplasia (BPD) is a common chronic lung disease in preterm infants characterized by alveolar simplicity, pulmonary microvascular dysplasia, and pulmonary interstitial fibrosis, atelectasis, and cystic transformation. As the survival rate of preterm infants increases, the risk of cardiac arrest increases. The incidence of BPD also has an increasing trend year by year. BPD can lead to chronic cardiopulmonary and nervous system sequelae, seriously affecting the survival rate and long-term quality of life of premature infants, and becoming one of the most intractable problems in NICU. In recent years, more and more literatures have reported that *Ureaplasma urealyticum* (UU) infection is related to the occurrence and development of BPD. In summary, this paper reviews the research progress on the relationship between bronchopulmonary dysplasia and Urealyticum.

Keywords

Bronchopulmonary Dysplasia, *Ureaplasma urealyticum*, Inflammation, Azithromycin

1. 概述

支气管肺发育不良(bronchopulmonary dysplasia, BPD)是早产儿最严重的并发症之一，给临床和公共卫生带来挑战。早在上世纪 60 年代 Northway 等人用 BPD 来描述一种需要长时间高氧及机械通气治疗的发生呼吸窘迫综合征的早产儿(胎龄多为 32~34 周)出现的慢性肺部疾病[1]。然而，我们现在所说的 BPD 是肺部在小管晚期或囊状发育阶段早期(即妊娠 28 周以下)暴露于宫外的结果[2] [3]，这导致肺泡和肺血管发育的改变，这种改变也可以在没有机械通气或高氧浓度的情况下发生。因此，当代对于 BPD 的看法是一种多因素导致的肺部疾病，遗传背景、产前暴露、极端早产和产后早期暴露共同导致了肺部不同程度的损伤和修复[2] [3]。

解脲脲原体是产前感染引发早产的主要病原体，多项研究表明其与 BPD 的发病机制有关[4] [5] [6] [7]。脲原体是女性生殖道中最常见的定植菌，胎儿或新生儿可能在产前通过宫内或胎盘感染、产时通过产道感染，以及产后的继发感染。早产儿中脲原体定植的发生率为 15%~36%。胎龄(GA)或出生体重(BW)越低，定殖率越高[7] [8] [9]。

迄今为止，许多研究探讨了脲原体与 BPD 之间的关系，但结论仍不明确[6] [8] [10] [11] [12]。我们仍然不能完全了解脲原体在 BPD 的发展中是否起主要作用，本文就支气管肺发育不良与解脲脲原体的关系的研究进展进行综述。

2. 解脲脲原体的毒性和免疫反应

解脲脲原体(*Ureaplasma urealyticum*, UU)是一种属于柔膜体纲支原体目支原体科脲原体属的微生物，没有细胞壁结构，是目前发现最小的、且能够进行自我复制和独立生存的微生物，UU 一共可以分成两个生物群和 14 个血清型，包括生物一群(parvum biovar 群)和生物二群(urealyticmu biovar 群)，以生物一群感染为主。UU 是一种机会致病菌，主要定植在泌尿生殖道和呼吸道粘膜表面，并进行复制，在成年女性

泌尿生殖道定植率高达 40%~80% [13]。特别是在妊娠期、卫生条件差、性伴侣多、使用口服避孕药的女性中定植率较高[14]。围生期 UU 感染主要通过母婴垂直传播，可通过上行感染、血行感染或产时通过产道感染[15]。

人感染 UU 后，UU 粘附于泌尿生殖道上皮细胞表面的受体上，一般不会进入组织和血液，当机体抵抗力降低或生殖道内微生态平衡被打破时，UU 可能会通过恶性因素导致肺泡壁细胞损伤。根据体外研究结果显示[16] [17]，首先，UU 激活了不同的 Toll 样受体。Toll 样家族受体主要在机体对病原的识别过程中发挥作用，可诱导肿瘤坏死因子 α、白细胞介素 6 的产生和 2 型肺上皮细胞和肺巨噬细胞的凋亡；其次，UU 感染宿主后与宿主免疫系统发生作用，产生广泛的异常免疫反应，包括激活 T 细胞和 B 细胞增殖，激活巨噬细胞、NK 细胞和细胞毒性 T 细胞的溶细胞活力，并能产生作用于多种器官的自身抗体，刺激淋巴细胞、单核细胞及巨噬细胞产生细胞因子，造成组织损伤[5]；体外模型表明，超因子蛋白 A (Surfactant protein-A (SP-A))是一种先天宿主防御分子，由肺分泌，可以吞噬和杀死 UU，但由于早产儿的 SP-A 浓度较低，导致早产儿肺部 UU 的清除延迟，使炎症细胞和促炎细胞因子表达增加[18]，造成肺损伤。第三，UU 含有尿素酶，可通过尿素的水解以产生 ATP，结合丝氨酸/苏氨酸激酶的释放，过氧化氢和磷脂酶会降解肺泡壁细胞的细胞膜，尿素的水解还会产生氨，引起 pH 值的变化，对细胞产生毒害作用[19]。以上综合因素最终导致了肺损伤。

3. 解脲脲原体与妊娠

脲原体是女性下生殖道最常见的定植菌，也能通过上行感染引起上生殖道的无症状感染。孕妇脲原体升高可引起绒毛膜眼膜炎，导致细胞因子和前列腺素的产生，并刺激子宫收缩，可造成女性妊娠期胚胎停育、反复流产；分娩前胎膜早破、胎儿窘迫、早产[13]；增加剖宫产率和产褥病率；新生儿易出现窒息、低出生体重、肺炎、血行感染、中枢感染、BPD、白细胞总数伴中性粒细胞数增加等，部分病人出现类白血病反应。除外早产与 BPD，UU 感染还与早产儿视网膜病(ROP)、颅内感染、颅内出血、新生儿坏死性小肠结肠炎和神经系统远期不良结局相关联[18] [20] [21] [22]，这些关联主要归因于 UU 引发的炎症反应。

4. 脲原体对肺发育的影响

脲原体感染对胎儿和新生儿肺发育的影响主要在绵羊和灵长类动物中进行了研究。在绵羊妊娠早期(150 天中的 55 天)羊膜内注射细小脲原体导致绒毛膜羊膜炎和肺脲原体部定植，并伴有中性粒细胞、单核细胞、IL-1β 和 IL-8 轻微增加[23]；在绵羊妊娠中期(第 80 天)羊膜内注射细小脲原体，会在 6 周后导致绒毛膜羊膜炎和轻度胎儿肺部炎症，这种肺部炎症会持续 9~10 周[24]；在绵羊在妊娠后期(110~121 天)羊膜内注射细小脲原体会引起轻度急性炎症反应，早产羊肺部中性粒细胞暂时增加[25]。在小鼠中，暴露于细小脲原体后肺部炎症反应具有自限性[26]。相比之下，在妊娠中期短暂暴露于细小脲原体的灵长类动物则会发生较强的肺部炎症反应[27]，感染脲原体的胎儿狒狒肺液中细胞因子表达增加，导致严重的毛细支气管炎和间质性肺炎[28]。此外，产前暴露于脲原体会影响宿主对产后刺激的反应。研究显示，绵羊产前暴露于脲原体会改变固有免疫系统，使未成熟的肺在出生后更容易受到炎症刺激[25]；对小鼠和狒狒的研究表明，它们对氧气和机械通气等产后刺激的反应也会增加[26] [28]。

非灵长类动物和灵长类动物之间的宿主反应不同，它们通过影响肺部炎症反应，从而使肺形态发生变化[5]。有研究表明，脲原体的刺激使非灵长类动物模型的肺泡或血管形态发生了改变[23] [26]。长期受脲原体刺激的绵羊肺成熟度增加，肺表面活性物质和肺容量增加[23]；中长期受脲原体刺激的绵羊表肺面活性物质增加，但肺容量没有变化[24]；短期受脲原体刺激的绵羊，细支气管和肺血管周围的弹性蛋白

减少，平滑肌增加，[25]弹性蛋白的减少导致肺简单化[29]。而非灵长类动物的这些肺部变化与脲原体的剂量或血清型无关[23]。与之相比，暴露于脲原体的灵长类动物(狒狒)的肺部改变比暴露于脲原体[5]的非灵长类动物(绵羊)的肺部改变更明显。在狒狒模型中，肺部急性炎症反应可以部分缓解，但上皮增生、肺泡壁增厚、纤维化和细支气管炎等结构变化仍然存在[27] [28] [30] [31]。与无法清除脲原体感染的狒狒相比，能够清除脲原体感染的狒狒对机械通气的呼吸需求较低，肺功能也得到改善[28]。

这些关于脲原体的临床前研究结果与细菌内毒素脂多糖(LPS)引起的绒毛膜羊膜炎的研究结果不同。注射 LPS 引起绒毛膜羊膜炎的动物比注射脲原体的动物炎症反应更强，肺部的炎症细胞如中性粒细胞、单核细胞、IL-1β [24] [32] [33]和巨噬细胞[34]的浓度更高。但 LPS 模型动物肺的形态没有持续的改变(如肺泡化减少等) [35]。

总之，临床前研究表明，与其他病因(如 LPS)引起的急性绒毛膜羊膜炎相比，脲原体引起的胎儿肺部的炎症反应较轻，但脲原体引起的肺结构性改变更多。有趣的是，长时间脲原体刺激引起肺结构改变持续时间较短，而短时间脲原体刺激引起的肺结构变化持续时间较长，这是脲原体独特的地方。

5. 合并 UU 感染的 BPD 的特点

研究表明，BPD 与遗传因素、肺发育不成熟、感染、氧中毒、机械通气肺损伤等多种因素有关[36]。其中，母孕期绒毛膜羊膜炎(chorioamnionitis, CAM)感染是 BPD 的独立危险因素。其中解脲脲原体 UU 是女性泌尿生殖道常见的定植微生物之一，也是引起 CAM 最常见的病原菌。文献报道，新生儿发生 UU 垂直传播的比例为 45%~66%，早产儿更高，很多不明原因的早产均因 UU 感染所致[37]。动物实验表明 UU 宫内定植会促使宫内胎儿促炎因子的表达增加[28]，胎肺胶原纤维增多[38]，发生类似 BPD 的病理改变。Cassell 等[39]对 200 例体重 ≤ 2500 g 早产儿气管内分泌物培养的研究，发现 UU 是分离出的最常见的单株微生物，UU 感染的新生儿患 BPD 的风险是未感染患儿的 2 倍。说明早产儿呼吸道 UU 定植与 BPD 发生风险升高有关。

有研究发现，有 CAM 感染病史的 BPD 相比于无围产期感染的 BPD，增加了早产儿 BPD 合并贫血、动脉导管未闭、呼吸窘迫综合征、脑室周围白质软化等疾病的发病率[40]。高拷贝数的 UU 定植相关的 CAM 可能导致更为严重的肺损伤，使中重度 BPD 发生率更高[41]；在 UU 定植的早产儿中，延迟治疗 UU 感染的患儿有创通气时间、用氧时间、及 BPD 发生率均显著高于早期治疗 UU 感染的患儿。这些均提示合并 UU 感染的 BPD 病情更重，合并症更多，住院时间更长。

6. UU 感染的治疗

由于 UU 没有细胞壁，干扰细胞壁合成的内酰胺及糖肽类抗生素对其治疗效果较差，因此，对于 UU 感染患者的治疗，应使用能够阻断 DNA 复制及感染蛋白质合成的抗菌药物。多数研究表明，大环内酯类抗生素能够有效清除 UU 感染，又能有效地抑制感染引发的系列炎症反应，而氟喹诺酮类抗生素和四环素类抗生素由于存在致畸作用，不推荐用于新生儿。因此，目前大环内酯类抗生素是治疗新生儿 UU 感染的首选药物。

既往观点认为红霉素是治疗 UU 感染的经典药物，但近年来多项研究表明，红霉素治疗 UU 感染效果欠佳，并且不能预防 BPD [42] [43]，这与 UU 对红霉素耐药有关[44]。有研究发现，阿奇霉素在肺中的药物浓度比红霉素高，体内和体外试验均证实，阿奇霉素对 UU 具有抗菌活性[45] [46] [47]，且优于红霉素[48]。有动物实验证实，相比红霉素，阿奇霉素可明显减轻小鼠肺部的炎症反应，其对 UU 的最小抑菌浓度(MIC)值最低，可直接抑制 UU 增殖，从而有效的清除 UU。对 UU 感染的早产儿进行研究，发现使用阿奇霉素组 BPD 的发生率明显降低[49]。Ballard 等[50]对 43 例超低出生体重儿进行了有关阿奇霉素疗

效的研究，发现阿奇霉素可减少撤机前激素的使用，并缩短患儿的住院时间。以上研究说明阿奇霉素可用于新生儿 UU 感染的治疗。但其治疗时机、使用途径、疗程等仍存在争议。

7. 讨论

解脲脲原体在 BPD 的发病机制中起着独特的作用。脲原体固有因素(毒力、细菌负荷量、暴露时间)和宿主因素(免疫反应、感染清除、早产程度、呼吸治疗需求、合并感染)之间的相互作用，以一种尚未完全明确的方式，促进了 BPD 的发展。

未来研究的一个挑战是诊断解脲脲原体感染。诊断脲原体的金标准是在专门的培养基中进行培养。由于脲原体缺乏细胞壁，因此对干燥和热高度敏感，标本需要立即送检，目前培养脲原体仍然很困难[51]。有人认为聚合酶链反应(PCR)和培养几乎同样有效[52] [53]，但也有人认为 PCR 更优[54]。PCR 试验的优点是可以鉴定脲原体种类，定量病原拷贝数，但与培养相比，PCR 的缺点是无法进行药敏试验。这两种检测的共同缺点是都不能区分携带者状态和感染。

最后，目前尚不清楚治疗脲原体感染/定植是否能有效减少肺部炎症，降低 BPD 发病率，并降低远期呼吸系统和神经系统并发症。未来的研究需要找到治疗孕妇及早产儿脲原体的最佳方法，理想的药物、给药方案、时间和给药途径仍然是一个有争议的问题。因此，早期识别 UU 感染相关 BPD 并找到有效的治疗措施可能是预防和治疗 BPD 的一个重要靶点。

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