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Hans汉斯

非伤寒沙门菌耐药和毒力机制的研究进展

杜歆闻[1]，杨桂花[2]

[1]吉首大学医学院，湖南 吉首
[2]张家界市人民医院小儿感染科，湖南 张家界

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摘 要

非伤寒沙门菌(NTS)是由多个血清型与流行克隆共同构成的疾病谱。多数NTS感染表现为自限性胃肠炎，但在婴幼儿、老年人、HIV感染者、近期疟疾患者、营养不良者及免疫功能低下人群中，易发展为侵袭性非伤寒沙门菌病(iNTS)，引发菌血症、脓毒症及肠外感染，临床常以发热为主要表现，胃肠道症状不突出。全球iNTS疾病负担以撒哈拉以南非洲地区最重，高危人群病死风险高。目前NTS耐药谱持续扩大，对喹诺酮/氟喹诺酮、第三代头孢菌素、多黏菌素及碳青霉烯类药物的耐药性已在多地检出。NTS的致病能力并非由单一毒力基因决定，而是由致病岛、III型分泌系统、黏附因子、毒力质粒、生物膜、胞内适应与免疫逃逸等多层机制共同调控。以非洲鼠伤寒沙门菌ST313为代表的高风险侵袭性克隆表明，高侵袭性与高耐药性并非独立演化，而是在克隆背景、移动遗传元件与调控网络共同作用下协同形成。本文在系统梳理NTS耐药与毒力机制的基础上，将ST313及非洲侵袭性S. Enteritidis克隆作为重点案例，讨论这些机制“是什么、为什么重要、还存在哪些不确定性”，并提出若干值得优先回答的关键科学问题。

关键词

非伤寒沙门菌，侵袭性非伤寒沙门菌病，ST313，耐药，毒力，致病岛，生物膜

Research Progress on the Drug Resistance and Virulence Mechanisms of Nontyphoidal Salmonella

Xinwen Du[1], Guihua Yang[2]

[1]College of Medicine, Jishou University, Jishou Hunan
[2]Department of Pediatric Infection, Zhangjiajie People’s Hospital, Zhangjiajie Hunan

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Abstract

Non-typhoidal Salmonella (NTS) constitutes a disease spectrum composed of multiple serotypes and epidemic clones. The majority of NTS infections present as self-limiting gastroenteritis, but in infants and young children, the elderly, HIV-infected individuals, recent malaria patients, malnourished individuals, and those with compromised immune systems, it can develop into invasive non-typhoidal Salmonella disease (iNTS), causing bacteremia, sepsis, and extraintestinal infections. Clinically, fever is the main manifestation, while gastrointestinal symptoms are not prominent. The global burden of iNTS is most severe in sub-Saharan Africa, with high mortality risks among high-risk populations. Currently, the drug resistance spectrum of NTS continues to expand, and resistance to quinolones/fluoroquinolones, third-generation cephalosporins, polymyxins, and carbapenems has been detected in many regions. The pathogenicity of NTS is not determined by a single virulence gene but is regulated by multiple mechanisms, including pathogenic islands, type III secretion systems, adhesion factors, virulence plasmids, biofilms, intracellular adaptation, and immune evasion. High-risk invasive clones represented by Salmonella Typhimurium ST313 in Africa indicate that high invasiveness and high drug resistance are not independently evolved but are formed in a coordinated manner under the combined influence of the clonal background, mobile genetic elements, and regulatory networks. Based on a systematic review of the drug resistance and virulence mechanisms of NTS, this article focuses on ST313 and invasive Salmonella Enteritidis clones in Africa as key cases to discuss "what they are, why they are important, and what uncertainties remain", and proposes several key scientific questions that deserve priority answers.

Keywords

Non-Typhoidal Salmonella, Invasive Non-Typhoidal Salmonella Disease, ST313, Drug Resistance, Virulence, Pathogenicity Island, Biofilm

1. 引言

非伤寒沙门菌(NTS)是除伤寒沙门菌和副伤寒沙门菌以外的多数沙门菌血清型的统称，由多种血清型、宿主适应型和流行克隆共同构成。在全球人源菌株中，肠炎沙门菌和鼠伤寒沙门菌最为常见，是 NTS 致病机制与临床研究的主要模型[1] [2]。NTS 感染多与污染食物、动物接触及食品链传播相关，临床表现以急性胃肠炎为主[1] [2]。在免疫功能低下人群中，细菌可突破肠道屏障进入血液，发展为 iNTS，往往以发热、菌血症和全身感染为主，部分患者可进一步出现骨关节、肺部、中枢神经系统等局灶性肠外感染。

全基因组研究显示，非洲流行的 S. Typhimurium ST313 以及两支非洲侵袭性 S. Enteritidis 克隆都表现出与典型胃肠炎相关克隆不同的基因组降解、前噬菌体组成、耐药质粒谱和代谢特征，提示 NTS 的真正高风险单位往往是“高危克隆”而不是宽泛的血清型名称[3]-[5]。这类观察之所以重要，在于它把分子机制与临床流行病学真正连接起来：为什么某些 NTS 更容易引起菌血症？为什么某些克隆更常合并多重耐药？为什么同属 S. Typhimurium，ST19 多见于胃肠炎而 ST313 却在非洲与 iNTS 高度相关？这些问题构成了当前 NTS 研究的核心。

2. 非伤寒沙门菌耐药机制

2.1. 喹诺酮和氟喹诺酮耐药

喹诺酮与氟喹诺酮类药物是治疗成人重症 NTS 感染的关键药物，其耐药主要由染色体靶点突变与质粒介导耐药共同驱动。NTS 对该类药物耐药的核心机制是 DNA 旋转酶与拓扑异构酶 IV 编码基因的喹诺酮耐药决定区(QRDR)突变，其中 gyrA 的 Ser83 和 Asp87 位点突变最常见，可导致萘啶酸耐药并降低环丙沙星敏感性；若叠加 parC、parE 或 gyrB 突变，耐药水平会阶梯式升高[6]-[8]。从临床角度看，这一机制的重要性不只在于“MIC 升高”，更在于它解释了为何部分分离株最初仅表现为敏感性下降，后续却能在持续用药压力下迅速演化为更高水平耐药[6] [9]。

而质粒介导喹诺酮耐药(PMQR)是促进高水平耐药形成的重要“跳板”。qnr 家族基因可保护 DNA 旋转酶和拓扑异构酶 IV，aac(6')-Ib-cr 可修饰部分氟喹诺酮药物，QepA 和 OqxAB 则与外排相关[10] [11]。这些机制单独存在时仅造成低水平耐药，但它们能够提高细菌在药物暴露下存活并进一步获得 QRDR 突变的概率[10]-[13]。此外，AcrAB-TolC 外排系统和 RamA 调控轴、以及 OmpC/OmpF 等孔蛋白改变，也会与 QRDR 突变共同塑造最终药敏表型[14] [15]。

现有证据提示，经典非洲 ST313 的标志性耐药负担首先是多重耐药和后续的 XDR 扩展，而并非所有流行株都已获得高水平氟喹诺酮耐药；但在 ST313 lineage II.1 中，已可见 IncHI2 质粒介导的 ESBL 和阿奇霉素耐药，并出现环丙沙星敏感性下降的菌株[16]。这提示一个更值得警惕的事实：当具有“血流侵袭优势”的克隆再叠加氟喹诺酮耐药演化时，其临床风险并不是简单相加，而是可能意味着经验治疗失效与播散能力并存。当前仍不清楚的是，ST313 特有的转录重编程、膜通透性调节和宿主内选择压力是否会改变其获得或维持氟喹诺酮耐药的代价；换言之，ST313 会不会比典型胃肠炎克隆更容易在保持侵袭性的同时耐受喹诺酮压力，仍缺乏直接答案。

2.2. β-内酰胺类及第三代头孢菌素耐药

第三代头孢菌素是儿童、孕妇及重症 NTS 感染的首选药物，其耐药性上升对临床救治影响显著。NTS 对第三代头孢菌素耐药的主要分子基础是产生 β 内酰胺酶，包括超广谱 β 内酰胺酶(ESBLs)与质粒介导的 AmpC 酶，常见酶型为 CTXM、TEM、SHV、CMY2 等，不同地区、血清型与克隆的主导酶型存在差异[17]-[20]。耐药基因通常位于可转移质粒上，如携带 blaCTXM1 的 IncI1 质粒、携带 blaCMY2 的 IncA/C2 质粒、IncHI2 多重耐药质粒等[21]-[23]。质粒的水平传播使第三代头孢菌素耐药常与氨基糖苷、磺胺、四环素、喹诺酮耐药共存，形成多重耐药，大幅压缩 iNTS 的治疗选择空间[19] [20]。

ST313 lineage 2 以多重耐药为特征，而 lineage II.1 在多重耐药基础上进一步获得 IncHI2 质粒介导的 ESBL 与阿奇霉素耐药，形成广泛耐药(XDR)表型[16]。非洲侵袭性 S. Enteritidis 克隆也显示出扩大的 MDR 质粒和独特前噬菌体组合[5]，提示侵袭性克隆与头孢耐药的共存并非偶然，而是由高危宿主环境、抗菌药物选择与可移动元件传播共同驱动的演化结果。目前仍不清楚的是，ESBL/AmpC 质粒在侵袭性克隆中究竟只是“附着的耐药货物”，还是会通过改变代谢成本、膜稳态甚至毒力基因表达来进一步塑造致病表型；这一问题对解释高危克隆的持续流行尤其关键。

2.3. 多黏菌素和碳青霉烯相关耐药

多黏菌素与碳青霉烯类是治疗多重耐药菌感染的最后防线，其耐药出现具有重大公共卫生意义。NTS 对多黏菌素的内源性耐药主要依赖脂多糖中脂质 A 的修饰，PmrA/PmrB 双组分调控系统可上调修饰基因，降低外膜负电荷，减少多黏菌素结合；PhoP/PhoQ 系统同时参与抗菌肽耐受与毒力调控，是连接耐药与宿主适应的重要通路[24]-[27]。

除染色体调控外，可转移的 mcr 基因是更具威胁的多黏菌素耐药机制。我国已在猪源、食品源及临床 NTS 中检出 mcr1、mcr3，且 mcr1 可与 ESBL 基因共存于同一质粒，一次水平转移即可同时获得对多黏菌素与 β 内酰胺类药物的耐药[28]-[31]。相比之下，碳青霉烯耐药在 NTS 中总体少见，但报道显示，OXA48 类碳青霉烯酶结合膜通透性下降，已可形成临床相关耐药[32]-[34]。

在 ST313 背景下，直接关于 mcr 或碳青霉烯酶在该克隆中广泛固定的证据目前仍然有限，但这并不意味着 ST313 与这一问题无关。相反，ST313 的研究恰恰提示我们要关注“共享通路”的风险：PhoP/PhoQ 和 PmrA/PmrB 既决定膜表面改造和抗菌肽耐受，也参与胞内适应；而 ST313 lineage 2 中一个位于 pgtE 启动子区的单核苷酸变异可提高外膜蛋白酶 PgtE 表达，增强补体因子 B 裂解和血清耐受[35]。PgtE 上调本身并不等于多黏菌素耐药，但它说明侵袭性克隆能够通过外膜和表面结构重塑显著提高体内生存优势。当前仍不清楚的是，这类为“血清抗性/宿主适应”所选择的膜改造，是否会同时降低多黏菌素敏感性，或者为 mcr 和碳青霉烯酶质粒的稳定维持提供背景优势；这正是未来必须重点监测的交叉区。

2.4. 移动遗传元件与多重耐药

NTS 多重耐药的形成高度依赖移动遗传元件，包括质粒、整合子、转座子与耐药岛。沙门菌基因岛 1 (SGI1)是最具代表性的模型，可携带氨苄西林、氯霉素、链霉素、磺胺、四环素耐药基因，形成 ACSSuT 多重耐药表型[36] [37]，它提示 NTS 耐药并非零散基因点状累积，而常常是“耐药模块化整合”的结果。

更重要的是，移动遗传元件可同时携带耐药基因与毒力基因，形成耐药–毒力杂合载体。S. Dublin 中的新型杂合质粒可同时携带 spv 毒力操纵子与多类耐药基因，且可见 IS26 等插入序列参与质粒重组[38]。这类共载体在临床成功克隆中固定后，抗菌药物使用会间接选择毒力相关骨架，加速耐药与毒力的协同传播。

ST313 是理解这一机制的典型案例，其代表株 D23580 携带与经典 S. Typhimurium 毒力质粒 pSLT 同源但已被重塑的 pSLT-BT；该质粒包含 Tn21 样多重耐药插入元件，同时保留 spv 相关毒力背景[39] [40]。此外，D23580 还携带 ST313 特有的 pBT1 质粒，该质粒含有与菌体适应和质粒维持相关的关键功能，如质粒编码 cysS 等[41]；其染色体上又携带 BTP1 和 BTP5 等特有前噬菌体[42]。因此，ST313 的“高侵袭性、高耐药性”并不能用单一基因解释，而更像是由染色体、毒力/耐药杂合质粒、额外适应性质粒和前噬菌体共同构成的网络化表型。当前最大的不确定性在于，这些元件之间的上位性互作究竟如何影响体内竞争、水平传播和抗菌药物选择下的稳定性；如果只停留在“检出某基因”，就无法真正判断一个克隆的临床危险性。

2.5. 非遗传性耐药：生物膜、持留菌和胞内存活

非遗传性耐药本质是细菌的耐受或持留状态，不涉及稳定遗传突变，而是通过生理状态重塑逃避药物杀伤[43]。沙门菌被巨噬细胞吞噬后，可形成不复制的持留菌亚群，吞噬泡酸化与营养限制是主要诱导因素，毒素抗毒素系统参与持留状态建立[44] [45]，可解释药敏敏感患者出现感染复发与治疗后排菌的现象。

生物膜是另一类重要的非遗传性耐清除机制。沙门菌生物膜主要由 curli 菌毛、纤维素、BapA 与胞外 DNA 构成，CsgD 为核心调控因子[46]-[48]。生物膜形成后，药物扩散受限、细菌代谢速率降低，显著提高对抗菌药物、消毒剂的耐受性[43] [47]。胆道与胆石表面的生物膜是持续带菌与反复感染的重要原因[49] [50]。

ST313 的特征修正了传统认知，其典型生物膜形成能力减弱，环境生存能力弱于普通 ST19 菌株[40]。这表明侵袭性克隆的适应重点并非环境表面生存，而是宿主内持留，依赖巨噬细胞内生存、免疫逃逸实

现播散。Van Puyvelde 等报道的 ST313 XDR 亚系还显示出生物膜形成和代谢能力改变[16]。当前真正未知的问题不是“ST313 会不会形成生物膜”，而是其在体内和体外不同生态位中究竟采用何种持留策略，以及这种策略如何影响复发、排菌和传播。

3. 非伤寒沙门菌毒力机制

3.1. 致病岛和 III 型分泌系统

NTS 毒力的核心框架是沙门菌致病岛(SPIs)与 III 型分泌系统(T3SS)。SPI1 主要介导肠上皮侵袭，其编码的 T3SS 可将效应蛋白注入宿主细胞，诱导肌动蛋白重塑，使细菌侵入上皮细胞[51] [52]；SPI2 主要负责系统感染阶段的胞内生存与扩散[51]-[53]，可重塑沙门菌含菌空泡，干扰吞噬体成熟，帮助细菌在巨噬细胞内存活并向全身播散[54]-[56]。这套系统决定了 NTS 是停留在肠腔，还是转入系统性感染阶段。

同时，沙门菌还可主动利用肠道炎症，破坏共生菌群的定植抵抗，利用四硫代物等作为电子受体进行厌氧呼吸，在炎症环境中获得竞争优势[57] [58]。NTS 致病并非简单的入侵炎症清除过程，而是病原体主动调控炎症强度、抢占代谢生态位的动态过程。

ST313 并未产生全新的毒力装置，而是对原有系统进行重编程。与普通 ST19 相比，ST313 保留了 SPI1、SPI2 核心结构，但转录模式、代谢程序与肠道致病特征发生改变，使同一套分泌系统更适配血流感染[3] [39]。未来研究重点是明确调控变化如何导致不同临床结局。

3.2. 黏附、定植与运动

NTS 致病的起始步骤是有效黏附与定植，依靠多种表面结构协同完成。I 型菌毛、长极菌毛、质粒编码菌毛、Std 菌毛、curli 菌毛等可参与宿主上皮、黏液层及糖基化受体的结合[59] [60]；Std 菌毛与宿主岩藻糖的相互作用可增强炎症并延长定植时间[61]；SPI4 编码的 SiiE 黏附蛋白、BapA 蛋白也参与定植过程[48] [62] [63]。

鞭毛与趋化系统可帮助细菌接近肠黏膜，但鞭毛易被免疫系统识别，因此细菌需要在运动侵袭与免疫逃逸之间保持平衡[64]，这也是侵袭性克隆与普通肠炎克隆的重要区别。

ST313 的定植播散模式与普通菌株显著不同。在鸡模型中，ST313 肠道定植能力较弱，但更快侵入肝脾造成全身感染[65]；体外研究显示，ST313 鞭毛介导的炎症诱导能力天然减弱[66]。这直接解释了临床中 ST313“腹泻不突出、菌血症严重”的表型，当前尚不清楚的是，这些黏附/运动性重编程究竟是细菌自身进化的主动适应，还是高危宿主背景下被动筛选的结果；此外，不同 ST313 亚系之间是否共享同一套定植－播散平衡策略，也仍需更精细的比较研究。

3.3. 毒力质粒和 spv 操纵子

部分 NTS 携带与系统感染密切相关的毒力质粒，其核心为 spvRABCD 操纵子[67]。SpvR 为调控因子，spvABCD 可提升细菌在宿主网状内皮系统中的存活与扩散能力。SpvB 可修饰肌动蛋白破坏细胞骨架，spvC 可抑制 MAPK 炎症通路，降低宿主免疫反应[68]-[70]。ST313 的 pSLTBT 质粒打破了毒力质粒与耐药质粒的传统界限，在经典毒力骨架上整合了多重耐药元件[39] [40]，且耐药元件插入可改变周边基因表达[39]。这意味着抗菌药物使用会无意中选择携带毒力骨架的耐药质粒，加速侵袭性克隆的传播与维持。

3.4. 生物膜形成与持续感染

生物膜是 NTS 环境存活、持续感染与传播的重要形式，其基质通常由 curli、纤维素、BapA、胞外

DNA 等多种组分共同构成，CsgD 是上游关键调控因子[46]-[48]。生物膜形成后，细菌不再只是简单聚集，而是进入一种更利于群体长期存活的组织化状态：药物扩散受限、养分与氧张力形成微环境梯度、部分细胞进入低代谢或持留状态，从而提高对干燥、消毒和抗菌药物暴露的耐受性[43] [47]。在临床层面，胆道、胆石等局部表面的沙门菌生物膜与持续带菌和反复感染直接相关[49] [50]。

但 ST313 提示，侵袭性克隆的持续感染不依赖强环境生物膜。D23580 的多细胞行为减弱表明，一些高危侵袭性克隆可能并不追求最大化环境表面生存，而是把适应重点转向宿主体内的免疫规避和细胞内复制[40]。NTS 持续感染的核心并非生物膜强弱，而是对特定生态位的持留策略适应。目前缺乏 ST313 临床样本的生物膜相关研究，限制了对其慢性化机制的理解。

3.5. 免疫逃逸与胞内适应

NTS 能否引发全身感染，关键在于进入宿主后能否逃避免疫清除。AvrA 效应蛋白可稳定肠道屏障、抑制炎症与凋亡[71] [72]；SpvC 可降低促炎因子水平、减少中性粒细胞浸润，促进全身播散[69] [70]；PhoP/PhoQ、PmrA/PmrB 系统参与膜修饰与巨噬细胞内环境适应[26] [27]。

ST313 的免疫逃逸机制具有代表性：pgtE 启动子突变增强补体耐受，助力血流生存[35]；ribB 过表达可逃避 MAIT 细胞识别[73]；特有前噬菌体编码基因可改变 O 抗原结构，bstA 基因则发挥“抗毒力”作用，精细调控毒力水平[42] [74] [75]。ST313 的成功并非依靠单一毒力基因，而是一套优化血流生存、降低免疫识别的调控网络。其与 HIV、疟疾、营养不良等宿主状态的相互作用，是高致死性的关键原因。

3.6. 高危侵袭性克隆的适应性进化

近年来关于高危侵袭性 NTS 克隆的研究显示，不同流行克隆的致病特征并不相同。ST313 是最典型的例子：其两个经典非洲流行谱系与撒哈拉以南非洲 iNTS 流行密切相关，并在时间上与 HIV 流行和抗菌药物使用增强存在关联[3]。与 ST19 相比，ST313 表现出更明显的基因组降解、代谢重塑和被修改的 enteropathogenesis，提示其正朝更适于系统播散的方向演化[3] [4]。后续研究又发现，ST313 并非单一路线静止演化：一方面，lineage II.1 在 MDR 基础上继续获得 IncHI2 质粒，形成 ESBL/阿奇霉素耐药叠加的 XDR 亚系[16]；另一方面，Pulford 等又报道了在马拉维出现的全敏感 lineage 3，提示“侵袭性”并不完全依赖于 MDR [4]。这一点非常重要，因为它提醒我们：高侵袭性和高耐药性常常在现实流行中同现，但二者并非绝对绑定，不能把 ST313 简单等同于“因为耐药所以侵袭”。

与 ST313 相呼应，非洲侵袭性 S. Enteritidis 克隆也显示出基因组降解、独特前噬菌体谱和扩大的 MDR 质粒[5]。这表明“从胃肠炎相关普通克隆向高侵袭性 iNTS 克隆转变”可能是一类可重复发生的演化现象，而不是 ST313 的孤例。为什么重要？因为它把 NTS 研究的重点从单基因功能学推进到了“病原体谱系生态学”：真正决定公共卫生风险的，往往是哪些克隆能够在高危宿主背景、人群传播和药物选择压力中长期稳定存在。当前仍不清楚的是，这种适应性进化究竟主要由宿主驱动、抗菌药物驱动，还是由传播方式和动物/环境储存库变化共同决定；不同地区 ST313 与非 ST313 克隆的并存也说明，这一过程并没有单一答案。

4. 耐药与毒力的关系

过去常把耐药与毒力视为彼此独立的问题，但现有证据更支持“条件性耦合”而非简单正负相关。其一，某些耐药获得确实会带来适应性代价。高水平氟喹诺酮耐药鼠伤寒沙门菌模型中，除多位点 QRDR 变化外，还可观察到侵袭基因下调、侵袭能力减弱和生长受损；其他研究亦显示，喹诺酮耐药与 invA 和 avrA 转录下降、上皮侵袭和胞内生存能力减弱有关[15] [76]。这类结果说明，在单个突变株层面，“更耐药”未必意味着“更有毒”。

其二，流行层面的答案又常常相反。移动遗传元件可以把耐药和毒力共同装载到一个成功骨架上，例如 S. Dublin 杂合质粒可同时携带 spv 操纵子和多类耐药基因[38]。ST313 中的 pSLT-BT 也提示，MDR 元件可整合到毒力质粒背景中并在侵袭性克隆内被长期保留[39] [40]；而 lineage II.1 进一步获得 IncHI2 质粒后形成 XDR，则说明高危克隆可以在不丧失侵袭优势的前提下持续累加耐药负担[16]。因此，在真实流行克隆层面，细菌完全可能通过载体重配、代价补偿和克隆筛选，实现“耐药与较强致病性并存”。

其三，耐药与毒力之间还存在一个常被忽视的中间层：持留菌、生物膜和胞内持续感染[43] [44] [47]。这些状态未必抬高 MIC，却显著增加了在药物压力和宿主免疫压力下的生存机会，进而促成复发、慢性感染和持续传播。对 ST313 而言，这种桥梁意义尤为突出：它一方面表现出环境多细胞行为减弱，另一方面又通过免疫逃逸、血清耐受和胞内复制强化系统播散[35] [40] [73]。这提示我们，临床上真正难以控制的并不总是“最耐药”或“毒力基因最多”的菌株，而是那些能够在特定宿主背景下同时优化播散、存活和治疗逃逸的克隆。

最后还应强调，耐药–毒力关系高度依赖遗传背景。ST313 lineage 3 的出现尤其具有启发性：它可以是全敏感的，却依然具有侵袭性相关谱系特征[4]。这说明侵袭性不能被简化为耐药的副产物；同样，耐药也不能被简化为毒力增强的充分条件。对风险评估而言，单看“耐药率”或“毒力基因数量”都远远不够，必须把克隆背景、质粒类型、前噬菌体组成、宿主状态和临床表型放在一起解释。

5. 知识空白与关键科学问题

(1) ST313 从“肠炎相关 S. Typhimurium 背景”向“血流侵袭性 pathovar”转变的最小因果变异集是什么？现有研究已经指出了基因组降解、启动子区 SNP、代谢缺陷、前噬菌体获得和转录重编程等多层变化[3] [4] [39]，但真正直接决定“更易菌血症、较少腹泻”的关键因果节点仍未被完全拆解。未来需要在等基因背景中逐个验证非编码变异、假基因形成与调控网络重排的独立和联合作用。

(2) pSLT-BT、pBT1、IncHI2 质粒以及 BTP1/BTP5 前噬菌体与染色体调控网络之间，究竟存在怎样的上位性互作？ST313 提示“高侵袭性、高耐药性”是多载体共同塑造的网络表型，而不是单个基因效果的线性相加[16] [39] [41] [42]。但目前我们仍缺少能够同时分辨载体存在/缺失、宿主体内适应、转录组变化和功能输出的系统研究。

(3) 侵袭性 NTS 克隆是否更倾向于形成“巨噬细胞内持留”而非“环境表面生物膜”，以及这两类持久化策略是否存在可预测的临床后果？ST313 多细胞行为减弱，但其系统播散和宿主内生存增强[40]；这提示不同克隆可能把资源投入到不同的持久化生态位。未来需要把患者来源菌株的单细胞层面胞内命运、复发风险和排菌时程联系起来，而不是只在体外做静态生物膜比较。

(4) HIV、疟疾、营养不良、肠道菌群破坏和抗菌药物暴露，分别在多大程度上是“放大疾病严重度”的宿主因素，又在多大程度上是“筛选侵袭性克隆”的生态因素？当前许多研究能够证明这些宿主背景与 iNTS 风险相关[9] [77]，但尚不能区分它们主要改变的是宿主易感性、细菌传播优势，还是两者兼有。这个问题如果不解决，就难以真正解释为什么 ST313 及类似克隆会在特定地区长期占优。

(5) 能否建立“长读长全基因组测序 + 转录组 + 表型组学”的临床预警框架，用于预测 NTS 的治疗失败、复发和侵袭风险？单纯依赖血清型、常规药敏或有限基因检测，已不足以识别高危克隆。特别是面对 ST313 这类同时涉及质粒、前噬菌体、调控变异和宿主适应的病原体，未来需要把基因、载体、克隆与临床结局进行真正的前瞻性整合。

6. 结语

总体而言，NTS 研究正在从“单个基因解释单个表型”转向“克隆–载体–调控网络–宿主背景共

同决定结局”的综合框架。ST313 及非洲侵袭性 S. Enteritidis 克隆表明，所谓“高侵袭性、高耐药性”并不是简单标签，而是多层分子改变在特定流行病学场景中的综合产物[3]-[5] [16]。随着 iNTS-GMMA 候选疫苗已进入早期人体研究[78]，对这些高危克隆分子基础的精细解析，不仅关系到机制认知，也将直接影响监测策略、风险分层和未来干预路径。

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