中国药业
China Pharmaceuticals

2024年9月5日 第33卷第17期
Vol. 33, No. 17, September 5, 2024

中图分类号:R975　　文献标志码:A　　文章编号:1006－4931(2024)17－0152－06
doi:10.3969/j.issn.1006－4931.2024.17.036

儿童非伤寒沙门菌胃肠炎抗感染治疗研究进展*

李高芬[1],李　俊[2],邱秀燕[1],杨　雅[2△]

(1. 中国人民解放军陆军军医大学第二附属医院,重庆　400037;　2. 重庆医科大学附属儿童医院·国家儿童健康与疾病临床医学研究中心·儿童发育疾病研究教育部重点实验室·儿童感染与免疫罕见病重庆市重点实验室,重庆　401122)

摘要:目的　为儿童非伤寒沙门菌(NTS)胃肠炎抗感染治疗提供参考。**方法**　采用计算机检索PubMed,Web of Science,The Cochrane Library和中国知网数据库中自建库起至2023年12月的儿童NTS胃肠炎抗感染治疗相关文献,从NTS的微生物学特点、流行病学、耐药性及抗感染治疗方案进行总结。**结果**　儿童是NTS感染的高危人群;在非免疫缺陷情况下,儿童NTS胃肠炎感染程度通常较轻,具有自限性,无须治疗;重度感染、新生儿和低于3月龄、先天性或医源性免疫缺陷患儿需抗感染治疗。目前,第3代头孢菌素、喹诺酮类和大环内酯类抗菌药物为主要治疗药物,具体用法用量应遵循相关指南,疗程以7～10 d为宜。**结论**　应严格把握儿童NTS胃肠炎抗感染治疗指征,制订合理的抗感染治疗方案,以规范抗菌药物的合理使用,遏制细菌耐药。

关键词:儿童;非伤寒沙门菌;胃肠炎;抗感染;进展

Research Progress on Anti－Infective Treatment of Non－Typhoid *Salmonella* Gastroenteritis in Children

LI Gaofen[1], *LI Jun*[2], *QIU Xiuyan*[1], *YANG Ya*[2]

(1. The Second Affiliated Hospital of Army Medical University, Chongqing, China　400037;　2. Children's Hospital of Chongqing Medical University · National Clinical Research Center for Child Health and Disorders · Ministry of Education Key Laboratory of Child Development and Disorders · Chongqing Key Laboratory of Child Rare Diseases in Infection and Immunity, Chongqing, China　401122)

Abstract: Objective　To provide a reference for the anti－infective treatment of children with non－typhoidal *Salmonella* (NTS) gastroenteritis. **Methods**　The literature related to anti－infective treatment of children with NTS gastroenteritis in the PubMed, Web of Science, The Cochrane Library, and CNKI were searched from the inception of these databases to December 2023. The microbiological characteristics, epidemiology, drug resistance, and anti－infective treatment plans of NTS were summarized. **Results**　Children are at high risk of NTS infection. In the absence of immunodeficiency, NTS gastroenteritis infection in children is generally mild and self－limiting, without treatment. Anti－infective treatment were required for severe infections, newborns and infants less than three months, and children with congenital or iatrogenic immunodeficiency. At present, the third－generation cephalosporins, quinolone antibiotics and macrolides antibiotics are the main therapeutic drugs, and the specific usage and dosage should follow relevant guidelines. The recommended course of treatment is 7－10 d. **Conclusion**　It is necessary to strictly grasp the indications of anti－infective treatment of children with NTS gastroenteritis and formulate a reasonable anti－infective treatment plan to standardize the rational use of antibiotics, and curb antimicrobial resistance.

Key words: children; non－typhoidal *Salmonella*; gastroenteritis; anti－infective; progress

非伤寒沙门菌(NTS)是指除伤寒杆菌和副伤寒杆菌以外的沙门菌,是全球范围内食源性感染的主要细菌病原体。NTS会引起急性胃肠炎,临床表现主要为发热、腹痛、腹泻等[1]。儿童由于免疫系统未成熟,是沙门菌属感染的高危人群[2]。健康儿童的NTS感染通常仅限于胃肠道,具有自限性,无须干预。抗菌药物治疗NTS

*基金项目:重庆市科卫联合医学科研项目[2024MSXM177]。

第一作者:李高芬,女,大学本科,主管护师,研究方向为消化系统疾病护理,(电子信箱)13696451381@163.com。

△通信作者:杨雅,女,硕士研究生,副主任药师,研究方向为临床药学,(电子信箱)363309136@qq.com。

法同时测定化妆品中22种有毒挥发性有机溶剂残留[J]. 分析测试学报,2017,36(5):697－700.

[42] 陈　平,陆卫明. 吹扫捕集－GC/MS联用同时测定水中31种挥发性有机物[J]. 中国卫生检验杂志,2013,23(5):1096－1099.

[43] 金永灿,崔柱文,孔维松,等. 顶空固相微萃取－气相色谱法测定卷烟包装材料中残留溶剂[J]. 理化检验:化学分册,2011,47(12):1424－1426.

[44] 陈　超,刘　珊,梁健谋,等. 药用复合膜残留溶剂谱的建立与残留溶剂来源分析[J]. 药物分析杂志,2021,41(12):2159－2170.

(收稿日期:2023－03－28;修回日期:2024－02－23)

胃肠道感染仅适用于有侵袭性疾病危险因素的儿童，但由于儿童药物选择的局限性和NTS耐药性的增加，导致NTS治疗难度增加。在此，采用计算机检索了PubMed，Web of Science，The Cochrane Library和中国知网数据库中自建库起至2023年12月的儿童NTS胃肠炎抗感染治疗相关文献，总结了NTS的微生物学特点、流行病学、耐药性及抗感染治疗方案，为临床规范、合理开展抗感染治疗提供参考。现报道如下。

1 微生物学特点

NTS属革兰阴性、兼性厌氧肠杆菌科细菌，包括邦戈沙门菌和肠道沙门菌[3]。其中，邦戈沙门菌主要存在于冷血动物，在人类属罕见条件致病菌；肠道沙门菌可引起人类感染，根据生化、抗原和血清学特征可分为6个亚种，每个亚种包括不同的血清型[4]。目前，已鉴定出超过2 500种血清型[5-6]，其中2个重要血清型鼠伤寒沙门菌和肠炎沙门菌与NTS全球流行有关[7]。鼠伤寒沙门菌在我国被认为是引起NTS感染最常见的血清型，导致多地暴发。WANG等[8]的研究显示，2006年至2019年我国沙门菌优势血清型中鼠伤寒沙门菌分离比例总体呈上升趋势。KE等[9]的研究显示，2012年至2019年鼠伤寒沙门菌为宁波市某三级医院儿童中主要分离出的菌株。

2 流行病学

全球每年有9 000万例胃肠炎由非伤寒沙门菌引起，导致15.5万人死亡[10]。NTS是美国食源性病原体中第二大致病菌，也是食源性疾病住院和死亡的最大原因[11]。虽然多数NTS感染是自限性的，但美国农业部经济研究局预测每年NTS胃肠道感染会导致7.4万人次就诊、1.9万人次住院、378人死亡，以及与36.7亿美元的直接和间接成本相关，表明需到医院就诊的患者比例仍较高[12]。NTS是全球幼儿和免疫功能低下患者细菌感染的主要致病菌[10]。据世界卫生组织（WHO）报告，每年有5.5亿人患病，其中5岁以下患儿2.2亿人[13]。美国的一项研究发现，NTS是5岁以下儿童最常见分离出的细菌性肠道病原体（42%）[14]。香港某医院分析了10年NTS感染的住院病例，发现4 828例住院患者中，15岁以下儿童占88.1%[15]。NTS仍是台湾地区儿童细菌性小肠结肠炎需住院治疗的主要病原体[16]。NTS在上海市儿童急性肠炎中的分离率为17.2%，超过弯曲菌属（7.1%）和志贺菌属（5.7%）[17]。可见，儿童为NTS感染的主要群体，应引起高度重视。

3 耐药性

3.1 耐药现状

NTS胃肠炎常用治疗药物包括氨苄西林、甲氧苄啶磺胺甲噁唑（TPM/SMX）、氯霉素等一线治疗药物，以及氟喹诺酮类、第3代头孢菌素、大环内酯类、碳青霉烯类抗菌药物。与抗菌药物敏感的NTS感染相比，耐药的NTS感染会导致更严重的疾病和不良结局，故应密切监测NTS分离菌株对上述药物的耐药性。

20世纪60年代初，首次报道了沙门菌对氯霉素耐药，随后关于1种或多种抗菌药物耐药的NTS血清型分离报道不断增加[18]。近年来，NTS对氨苄西林、TPM/SMX、氯霉素等药物普遍耐药[17]，呈多重耐药趋势。广州市从化区NTS感染患者多重耐药率达47.06%[19]，福建省2012年至2021年的NTS多重耐药率达60.1%[20]，表明我国NTS已呈多重耐药形势，对控制或预防NTS提出了重大挑战。

由于NTS对上述一线治疗药物普遍耐药，头孢菌素（如头孢曲松）和氟喹诺酮类抗菌药物（如环丙沙星）已被推荐作为主要治疗药物[21]。随着抗菌药物的广泛使用，NTS对头孢菌素和喹诺酮类抗菌药物也出现了耐药性，但不同国家的耐药性存在差异。美国头孢曲松耐药率约为3.5%，非洲头孢菌素耐药率约为5%，欧洲头孢噻肟耐药率约为1.8%[22]。我国广东省5岁以下儿童NTS分离菌株对头孢吡肟、头孢噻肟、头孢他啶的耐药率分别为8.9%，15.6%，6.2%[23]。福建省儿童NTS分离菌株对头孢曲松和头孢他啶的耐药率分别为24.5%和14.6%[24]。氟喹诺酮类抗菌药物虽禁用于18岁以下儿童，但随着第3代头孢菌素耐药率的升高，该类药物也成为NTS致感染性腹泻的主要治疗药物，但其耐药率也逐渐升高。一项针对澳大利亚1995年至2015年NTS的耐药情况分析发现，NTS对环丙沙星的耐药率由0.1%升至7.8%[25]。我国广东省和福建省对环丙沙星的耐药率分别为6.6%[23]和15.8%[20]，不断升高的细菌耐药率给临床治疗带了极大困难。

目前，碳青霉烯类抗菌药物和阿奇霉素被认为是多重耐药和广泛耐药菌株引起的侵袭性NTS感染的最后治疗选择[21,26]。但一项全球系统评价发现，1972年至2018年，NTS对阿奇霉素的耐药率为2.1%[27]。2014年至2021年，深圳儿童医院肠道沙门菌对阿奇霉素的耐药率为3.08%[28]。台湾地区NTS分离菌株对阿奇霉素的耐药率为3.1%，远高于欧洲和美国[29]，表明NTS对阿奇霉素的耐药率呈上升趋势。故有必要了解阿奇霉素的耐药情况，以正确选择抗菌药物。虽然碳青霉烯类抗菌药物耐药在NTS中仍少见，但已在人类、动物和食物中发现了这种耐药的分离菌株[30]，故也应引起重视。

3.2 耐药机制

NTS的耐药机制主要包括获取耐药质粒、抗菌药物结合位点突变或缺失降低靶向抗菌药物的敏感性和主动外排泵等。明确NTS对各种抗菌药物的耐药机制，对

于选择抗感染治疗方案具有重要意义。

第3代头孢菌素的耐药机制包括产超广谱β-内酰胺酶(ESBLs)或AmpC酶[31],其中CTX-M-1是最常见的ESBLs类型[31-32],还有CTX-M-14和blaCTX-M-65等[33-34]。ESBLs和AmpC酶基因通常位于质粒,通过水平基因转移在肠杆菌属和种之间传播[35]。

喹诺酮类抗菌药物耐药机制主要包括DNA促旋酶和拓扑异构酶Ⅳ决定区域的位点突变[20,36],以及质粒介导的耐药基因qnr和oqxAB[37-38]。

阿奇霉素的耐药机制包括药物被Mph(A)修饰,大环内酯29-磷酸转移酶[39],23S rRNA被ErmB和Erm42甲基化,rRNA腺嘌呤*N*-6-甲基转移酶[40-41],以及药物被AcrB中有R717突变的AcrAB-TolC外排泵排出增加[42]。耐药基因可由质粒[43]、转座子(包括整合和接合元件)[44]和染色体[45]携带及传递。

碳青霉烯类抗菌药物的耐药机制主要包括产碳青霉烯酶和膜孔蛋白缺失。与其他肠杆菌科细菌(如大肠埃希菌)相比,从人类样本中分离出的碳青霉烯耐药NTS很少,但已有多个国家报道NTS会产生5种具有重要临床意义的碳青霉烯酶,即肺炎克雷伯菌碳青霉烯酶(KPC)、亚胺培南酶(IMP)、新德里金属-β-内酰胺酶(NDM)、维罗那整合子编码的金属-β-内酰胺酶(VIM)和苯唑西林酶(OXA-48),这是导致NTS对碳青霉烯类抗菌药物耐药的主要机制[21,30]。多数沙门菌血清型携带7种膜孔蛋白,其中ompC_378和ompD缺失是碳青霉烯类抗菌药物耐药的关键膜孔蛋白[46],这是NTS对碳青霉烯类抗菌药物耐药的重要机制。

另外,磺胺类抗菌药物的耐药机制主要为质粒转移。BAKKEREN等[47]的研究显示,沙门菌持留菌促进抗菌药物耐药质粒在肠道内的传播成为另一耐药机制,这是由于组织相关的沙门菌持留菌可作为耐药质粒的储存库,促进细菌耐药性在肠道内传播,也揭示了持留菌的持续存在不仅会导致感染疾病的反复发作,还能促进耐药性的传播。

4 抗感染治疗方案

4.1 适应证

由于NTS胃肠炎具有自限性,不推荐确诊为NTS胃肠炎、症状为轻度至中度的12月龄至18岁免疫功能正常的患儿使用抗菌药物治疗。ONWUEZOBE等[48]的研究显示,抗菌药物治疗对病程长短、腹泻时间和发热时间均无显著改善,而NTS胃肠炎过度使用抗菌药物可能增加抗菌药物不良反应和NTS耐药性,还可能延长无症状携带状态的风险[49-50]。

NTS胃肠炎患儿使用抗菌药物抗感染治疗的适应证仍存在争议,目前主要通过疾病严重程度评估、免疫因素、年龄因素等选择抗菌药物。ONWUEZOBE等[48]的研究建议,NTS胃肠炎抗感染治疗指征为诊断NTS胃肠炎的3~6个月或免疫功能低下的婴儿。COHEN等[51]研究认为,NTS胃肠炎患者应在有发生侵袭性沙门菌病或继发性病灶的风险时使用抗菌药物治疗,包括重度感染如高热或持续发热、严重腹泻、C反应蛋白升高等症状、新生儿和低于3月龄的婴儿、先天性或医源性免疫缺陷。NAIR等[52]研究指出,推荐怀疑或确诊为侵袭性感染(免疫缺陷、慢性基础疾病和严重肠炎)的低于3月龄患儿采用抗感染治疗。因此,应严格把握NTS胃肠炎患儿的抗感染治疗适应证,避免药物滥用而导致耐药性增加。

4.2 抗菌药物选择与用法用量

由于氨苄西林、TPM/SMX和氯霉素的耐药率较高,已不作为NTS胃肠炎的一线治疗药物。氨基苷类药物虽有良好的体外活性,但临床疗效不佳,也不推荐使用[49]。不同指南推荐治疗NTS胃肠炎的抗菌药物存在差异,但主要以第3代头孢菌素、喹诺酮类和大环内酯类抗菌药物为主。

第3代头孢菌素:是目前治疗儿童NTS感染的首选药物。NTS的细胞内特性可能影响细胞外浓度较高的抗菌药物发挥作用,第3代头孢菌素如头孢曲松具有胞内渗透作用,胞内活性依赖于胞外浓度[53]。因此,第3代头孢菌素治疗侵袭性局灶性感染的剂量应比常规使用剂量高,如头孢曲松应予100 mg/(kg·d)。若第3代头孢菌素耐药,可选择酶抑制剂如哌拉西林他唑巴坦和头孢哌酮舒巴坦[54],可能因为头孢菌素耐药的主要机制是产生AmpCβ-内酰胺酶和ESBLs。根据指南,可选择头孢曲松50 mg/(kg·d)[51]、20~100 mg/(kg·d)[54]、50~100 mg/(kg·d)[55],静脉滴注(ivgtt),每日1次,不超过2 g/d[51]或20~80 mg/(kg·d),ivgtt,每日1~2次[56];头孢噻肟50~100 mg/(kg·d),ivgtt,每日2~4次[54,56];头孢他啶30~100 mg/(kg·d),ivgtt,每日2~3次[54,56];哌拉西林他唑巴坦60~150 mg/(kg·d),ivgtt,每日3~4次[54];头孢哌酮50~200 mg/(kg·d),ivgtt,每日2~3次[56]。

喹诺酮类抗菌药物:在巨噬细胞和多形核细胞中的浓度较高,是治疗NTS的主要药物[53]。但用于发育中的动物时观察到软骨异常,避免用于儿童,但有证据表明此类药物可短期用于儿童[57]。目前,临床仅在充分论证后,作为NTS胃肠炎患儿对第3代头孢菌素耐药的替代治疗药物。可选择环丙沙星20 mg/(kg·d),ivgtt,每日2次或30 mg/(kg·d),口服,每日2次,不超过1 500 mg/d[51]。

阿奇霉素:在巨噬细胞和多形核细胞中的浓度较高[53,58],在吞噬细胞中的浓度至少较血浆高出200倍[52]。

体外研究表明，其在根除细胞内 NTS 方面比β－内酰胺类等抗菌药物更有效[51]。由于阿奇霉素的药物敏感性试验中缺乏标准化的临界值，故未常规应用，但其体外抗 NTS 活性较好[59]。虽然很难证实抗菌药物最低抑菌浓度的临床疗效和体外活性与显著的细胞内蓄积相关，但具有细胞内活性的药物仍常被推荐，尤其是对于免疫功能低下的患者[60]。可选择 20 mg /（kg·d），口服，每日 1 次，不超过 500 mg / d[51]或 10 mg /（kg·d），ivgtt，每日 1 次[55]。

碳青霉烯类抗菌药物：是多重耐药和广泛耐药菌株引起侵袭性 NTS 感染的最后治疗选择[21,26]。美罗培南在体外对 NTS 有活性，在人巨噬细胞内可达到较高的细胞内浓度[61]。但目前使用碳青霉烯类抗菌药物治疗 NTS 感染的临床经验有限，仍需更多循证证据指导该药的合理使用。现有指南或共识中并未常规推荐碳青霉烯类抗菌药物作为治疗药物。

4.3 疗程

抗菌药物对 NTS 胃肠炎的最佳用药疗程尚不明确。ONWUEZOBE 等[48]的研究结果显示，NTS 胃肠炎的抗菌治疗持续时间为 3 ~ 14 d，多数采用 5 d 方案。台湾的一项对 59 例 NTS 菌血症患儿的回顾性研究认为，对于年龄为 1 岁、无局灶性肠外感染的 NTS 胃肠炎患儿，抗菌药物使用应少于 10 d[62]。该研究小组随后的 1 篇综述比较了年龄低于 18 岁儿童使用抗菌药物治疗 7 d 及以上对治疗结局的影响，发现治疗后 12 个月，两组均未发现转移性并发症或复发性疾病[63]。2023 年，法国发表的一篇儿童胃肠炎抗感染治疗综述推荐疗程为 3 ~ 5 d[51]。总体而言，对于 NTS 胃肠炎，无肠外侵袭性疾病时，推荐治疗疗程小于 7 d，延长治疗时间对降低复发或并发症无益，还可能增加耐药性和药品不良反应。

5 结语

随着抗菌药物的广泛应用，NTS 耐药率逐年上升，特别是大环内酯类和碳青霉烯类耐药菌株的出现，给 NTS 感染的治疗带来了严峻挑战。为防止多重耐药 NTS 的进一步传播，应严格把握儿童 NTS 胃肠炎抗感染治疗指征，制订合理的抗感染治疗方案，以规范抗菌药物的合理使用，遏制细菌耐药。

参考文献

[1] PARISI A, CRUMP JA, STAFFORD R, et al. Increasing incidence of invasive nontyphoidal *Salmonella* infections in Queensland, Australia, 2007 - 2016 [J]. PLoS Neglected Tropical Diseases, 2019, 13(3): e0007187.

[2] BULA - RUDAS FJ, RATHORE MH, MARAQA NF. *Salmonella* Infections in Childhood[J]. Advances in Pediatrics, 2015, 62(1): 29 - 58.

[3] CHLEBICZ A, SLIZEWSKA K. Campylobacteriosis, Salmonellosis, Yersiniosis, and Listeriosis as Zoonotic Foodborne Diseases: A Review[J]. International Journal of Environmental Research and Public Health, 2018, 15(5): 863.

[4] REEVES MW, EVINS GM, HEIBA AA, et al. Clonal nature of *Salmonella* typhi and its genetic relatedness to other salmonellae as shown by multilocus enzyme electrophoresis, and proposal of *Salmonella* bongori comb. nov [J]. Journal of Clinical Microbiology, 1989, 27(2): 313 - 320.

[5] GUIBOURDENCHE M, ROGGENTIN P, MIKOLEIT M, et al. Supplement 2003 - 2007 (No. 47) to the White - Kauffmann - Le Minor scheme[J]. Research in Microbiology, 2010, 161(1): 26 - 29.

[6] ACHTMAN M, WAIN J, WEILL FX, et al. Multilocus sequence typing as a replacement for serotyping in *Salmonella* enterica[J]. PLoS Pathogens, 2012, 8(6): e1002776.

[7] European Food Safety Authority, European Centre for Disease Prevention and Control. The European Union One Health 2019 Zoonoses Report[J]. EFSA J, 2021, 19(2): e06406.

[8] WANG Y, LIU Y, LYU N, et al. The temporal dynamics of antimicrobial - resistant *Salmonella* enterica and predominant serovars in China[J]. National Science Review, 2023, 10(3): nwac269.

[9] KE YF, LU WB, LIU WY, et al. Non - typhoidal *Salmonella* infections among children in a tertiary hospital in Ningbo, Zhejiang, China, 2012 - 2019[J]. PLoS Neglected Tropical Diseases, 2020, 14(10): e0008732.

[10] MAJOWICZ SE, MUSTO J, SCALLAN E, et al. The global burden of nontyphoidal *Salmonella* gastroenteritis [J]. Clinical Infectious Diseases, 2010, 50(6): 882 - 889.

[11] SCALLAN E, HOEKSTRA RM, ANGULO FJ, et al. Foodborne illness acquired in the United States: major pathogens[J]. Emerging Infectious Diseases, 2011, 17(1): 7 - 15.

[12] AGID O, FOUSSIAS G, REMINGTON G. Long - acting injectable antipsychotics in the treatment of schizophrenia: their role in relapse prevention[J]. Expert Opinion on Pharmacotherapy, 2010, 11(14): 2301 - 2317.

[13] BERWAERTS J, LIU Y, GOPAL S, et al. Efficacy and Safety of the 3 - Month Formulation of Paliperidone Palmitate *vs* Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial[J]. JAMA Psychiatry, 2015, 72(8): 830 - 839.

[14] SCALLAN E, MAHON BE, HOEKSTRA RM, et al. Estimates of illnesses, hospitalizations and deaths caused by major bacterial enteric pathogens in young children in the United States[J]. The Pediatric Infectious Disease Journal, 2013, 32(3): 217 - 221.

[15] WANG P, GOGGINS WB, CHAN EYY. Associations of *Salmonella* hospitalizations with ambient temperature, humidity and rainfall in Hong Kong[J]. Environment International, 2018, 120: 223 - 230.

[16] SU LH, CHIU CH. *Salmonella*: clinical importance and evolu-

tion of nomenclature[J]. Chang Gung Medical Journal, 2007, 30(3): 210 - 219.

[17] LI Y, XIE X, XU X, et al. Nontyphoidal *Salmonella* infection in children with acute gastroenteritis: prevalence, serotypes, and antimicrobial resistance in Shanghai, China [J]. Foodborne Pathogens and Disease, 2014, 11(3): 200 - 206.

[18] YOKE - KQUEEN C, LEARN - HAN L, NOORZALEHA AS, et al. Characterization of multiple - antimicrobial - resistant *Salmonella* enterica Subsp. enterica isolated from indigenous vegetables and poultry in Malaysia [J]. Letters in Applied Microbiology, 2008, 46(3): 318 - 324.

[19] GONG B, LI H, FENG Y, et al. Prevalence, Serotype Distribution and Antimicrobial Resistance of Non - Typhoidal *Salmonella* in Hospitalized Patients in Conghua District of Guangzhou, China[J]. Frontiers in Cellular and Infection Microbiology, 2022, 12: 805384.

[20] CHEN H, QIU H, ZHONG H, et al. Non - Typhoidal *Salmonella* Infections Among Children in Fuzhou, Fujian, China: A 10 - Year Retrospective Review from 2012 to 2021 [J]. Infection and Drug Resistance, 2023, 16: 2737 - 2749.

[21] CRUMP JA, SJOLUND - KARLSSON M, GORDON MA, et al. Epidemiology, Clinical Presentation, Laboratory Diagnosis, Antimicrobial Resistance, and Antimicrobial Management of Invasive *Salmonella* Infections [J]. Clinical Microbiology Reviews, 2015, 28(4): 901 - 937.

[22] TAKKINSATIAN P, SILPSKULSUK C, PROMMALIKIT O. Clinical features and antibiotic susceptibility of *Salmonella* gastroenteritis in children: A ten - year review[J]. The Medical Journal of Malaysia, 2020, 75(6): 672 - 676.

[23] LIANG Z, KE B, DENG X, et al. Serotypes, seasonal trends, and antibiotic resistance of non - typhoidal *Salmonella* from human patients in Guangdong Province, China, 2009 - 2012[J]. BMC Infectious Diseases, 2015, 15: 53.

[24] SONG W, SHAN Q, QIU Y, et al. Clinical profiles and antimicrobial resistance patterns of invasive *Salmonella* infections in children in China [J]. European Journal of Clinical Microbiology & Infectious Diseases, 2022, 41(10): 1215 - 1225.

[25] WILLIAMSON DA, LANE CR, EASTON M, et al. Increasing Antimicrobial Resistance in Nontyphoidal *Salmonella* Isolates in Australia from 1979 to 2015[J]. Antimicrobial Agents and Chemotherapy, 2018, 62(2): e02012 - 17.

[26] HUGHES MJ, BIRHANE MG, DOROUGH L, et al. Extensively Drug - Resistant Typhoid Fever in the United States[J]. Open Forum Infectious Diseases, 2021, 8(12): ofab572.

[27] MARCHELLO CS, CARR SD, CRUMP JA. A Systematic Review on Antimicrobial Resistance among *Salmonella* Typhi Worldwide [J]. The American Journal of Tropical Medicine and Hygiene, 2020, 103(6): 2518 - 2527.

[28] WANG H, CHENG H, HUANG B, et al. Characterization of resistance genes and plasmids from sick children caused by *Salmonella* enterica resistance to azithromycin in Shenzhen, China[J]. Frontiers in Cellular and Infection Microbiology, 2023, 13: 1116172.

[29] CHIOU CS, HONG YP, WANG YW, et al. Antimicrobial Resistance and Mechanisms of Azithromycin Resistance in Nontyphoidal *Salmonella* Isolates in Taiwan, 2017 to 2018 [J]. Microbiology Spectrum, 2023, 11(1): e0336422.

[30] FERNANDEZ J, GUERRA B, RODICIO MR. Resistance to Carbapenems in Non - Typhoidal *Salmonella* enterica Serovars from Humans, Animals and Food [J]. Veterinary Sciences, 2018, 5(2): 40

[31] HASMAN H, MEVIUS D, VELDMAN K, et al. Beta - lactamases among extended - spectrum beta - lactamase (ESBL) - resistant *Salmonella* from poultry, poultry products and human patients in The Netherlands [J]. The Journal of Antimicrobial Chemotherapy, 2005, 56(1): 115 - 121.

[32] ELLER C, SIMON S, MILLER T, et al. Presence of beta - lactamases in extended - spectrum - cephalosporin - resistant *Salmonella* enterica of 30 different serovars in Germany 2005 - 11 [J]. The Journal of Antimicrobial Chemotherapy, 2013, 68(9): 1978 - 1981.

[33] PIETSCH M, SIMON S, MEINEN A, et al. Third generation cephalosporin resistance in clinical non - typhoidal *Salmonella* enterica in Germany and emergence of bla_{CTX-M} - harbouring pESI plasmids [J]. Microbial Genomics, 2021, 7 (10): 000698.

[34] LIVERMORE DM. Beta - lactamase - mediated resistance and opportunities for its control[J]. The Journal of Antimicrobial Chemotherapy, 1998, 41(Suppl D): 25 - 41.

[35] ROZWANDOWICZ M, BROUWER MSM, FISCHER J, et al. Plasmids carrying antimicrobial resistance genes in Enterobacteriaceae [J]. The Journal of Antimicrobial Chemotherapy, 2018, 73(5): 1121 - 1137.

[36] PRIBUL BR, FESTIVO ML, DE SOUZA MM, et al. Characterization of quinolone resistance in *Salmonella spp.* isolates from food products and human samples in Brazil[J]. Brazilian Journal of Microbiology, 2016, 47(1): 196 - 201.

[37] LIN D, CHEN K, WAI - CHI CHAN E, et al. Increasing prevalence of ciprofloxacin - resistant food - borne *Salmonella* strains harboring multiple PMQR elements but not target gene mutations[J]. Scientific Reports, 2015, 5: 14754.

[38] WONG MH, CHEN S. First detection of oqxAB in *Salmonella spp.* isolated from food[J]. Antimicrobial Agents and Chemotherapy, 2013, 57(1): 658 - 660.

[39] NOGUCHI N, EMURA A, MATSUYAMA H, et al. Nucleotide sequence and characterization of erythromycin resistance determinant that encodes macrolide 2′ - phosphotransferase Ⅰ in *Escherichia coli*[J]. Antimicrobial Agents and Chemotherapy, 1995, 39(10): 2359 - 2363.

[40] DESMOLAIZE B, ROSE S, WARRASS R, et al. A novel Erm

monomethyltransferase in antibiotic - resistant isolates of *Mannheimia haemolytica* and *Pasteurella multocida* [J]. Molecular Microbiology, 2011, 80(1): 184 - 194.

[41] FARROW KA, LYRAS D, ROOD JI. The macrolide - lincosamide - streptogramin B resistance determinant from Clostridium difficile 630 contains two erm (B) genes [J]. Antimicrobial Agents and Chemotherapy, 2000, 44(2): 411 - 413.

[42] HOODA Y, SAJIB MSI, RAHMAN H, et al. Molecular mechanism of azithromycin resistance among typhoidal *Salmonella* strains in Bangladesh identified through passive pediatric surveillance[J]. PLoS Neglected Tropical Diseases, 2019, 13(11): e0007868.

[43] HONG YP, WANG YW, HUANG IH, et al. Genetic Relationships among Multidrug - Resistant *Salmonella enterica* Serovar Typhimurium Strains from Humans and Animals[J]. Antimicrobial Agents and Chemotherapy, 2018, 62(5): e00213 - 18.

[44] HONG YP, CHEN YT, WANG YW, et al. Integrative and Conjugative Element - Mediated Azithromycin Resistance in Multidrug - Resistant *Salmonella enterica* serovar Albany[J]. Antimicrobial Agents and Chemotherapy, 2023, 65(5): e02634 - 20.

[45] NAIR S, ASHTON P, DOUMITH M, et al. WGS for surveillance of antimicrobial resistance: a pilot study to detect the prevalence and mechanism of resistance to azithromycin in a UK population of non - typhoidal *Salmonella*[J]. The Journal of Antimicrobial Chemotherapy, 2016, 71(12): 3400 - 3408.

[46] HSU PC, WANG YW, CHEN BH, et al. Carbapenem resistance in extensively drug - resistant *Salmonella enterica* serovar Agona and AmpC beta - lactamase - producing *S*. Infantis[J]. Microbiology Spectrum, 2023, 11(6): e0292223.

[47] BAKKEREN E, HUISMAN JS, FATTINGER SA, et al. *Salmonella* persisters promote the spread of antibiotic resistance plasmids in the gut[J]. Nature, 2019, 573(7773): 276 - 280.

[48] ONWUEZOBE IA, OSHUN PO, ODIGWE CC. Antimicrobials for treating symptomatic non - typhoidal *Salmonella* infection[J]. The Cochrane Database of Systematic Reviews, 2012, 11(11): CD001167.

[49] HAEUSLER GM, CURTIS N. Non - typhoidal *Salmonella* in children: microbiology, epidemiology and treatment [J]. Advances in Experimental Medicine and Biology, 2013, 764: 13 - 26.

[50] HUANG IF, WAGENER MM, HSIEH KS, et al. Nontyphoid salmonellosis in taiwan children: clinical manifestations, outcome and antibiotic resistance[J]. Journal of Pediatric Gastroenterology and Nutrition, 2004, 38(5): 518 - 523.

[51] COHEN R, MINODIER P, HAU I, et al. Anti - infective treatment of gastro - intestinal tract infections in children [J]. Infectious Diseases Now, 2023, 53(8S): 104784.

[52] NAIR S, CHATTAWAY M, LANGRIDGE GC, et al. ESBL - producing strains isolated from imported cases of enteric fever in England and Wales reveal multiple chromosomal integrations of *bla*CTX - M - 15 in XDR *Salmonella* Typhi[J]. The Journal of Antimicrobial Chemotherapy, 2021, 76(6): 1459 - 1466.

[53] CHIU CH, LIN TY, OU JT. *In vitro* evaluation of intracellular activity of antibiotics against non - typhoid *Salmonella* [J]. International Journal of Antimicrobial Agents, 1999, 12(1): 47 - 52.

[54] 中华医学会儿科学分会消化学组,《中华儿科杂志》编辑委员会. 中国儿童急性感染性腹泻病临床实践指南[J]. 中华儿科杂志, 2016, 54(7): 483 - 488.

[55] GUARINO A, ASHKENAZI S, GENDREL D, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition / European Society for Pediatric Infectious Diseases evidence - based guidelines for the management of acute gastroenteritis in children in Europe: update 2014 [J]. Journal of Pediatric Gastroenterology and Nutrition, 2014, 59 (1): 132 - 152.

[56] 国家卫生健康委员会办公厅. 关于印发儿童急性感染性腹泻病诊疗规范(2020 年版)的通知[A/OL]. (2020 - 09 - 11) [2024 - 05 - 22]. http: // www. nhc. gov. cn / yzygj / s7659 / 202009 / 5c03bafd1db74fb68e2a74afa2ed08c1. shtml.

[57] BURKHARDT JE, WALTERSPIEL JN, SCHAAD UB. Quinolone arthropathy in animals versus children[J]. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 1997, 25(5): 1196 - 1204.

[58] PARNHAM MJ, ERAKOVIC HABER V, GIAMARELLOS - BOURBOULIS EJ, et al. Azithromycin: mechanisms of action and their relevance for clinical applications[J]. Pharmacology & Therapeutics, 2014, 143(2): 225 - 245.

[59] GUNELL M, KOTILAINEN P, JALAVA J, et al. *In vitro* activity of azithromycin against nontyphoidal *Salmonella enterica* [J]. Antimicrobial Agents and Chemotherapy, 2010, 54 (8): 3498 - 3501.

[60] GBD 2019 Mental Diisorders. Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990 - 2019: a systematic analysis for the Global Burden of Disease Study 2019[J]. The Lancet PsychIatry, 2022, 9(2): 137 - 150.

[61] LIU CY, HUANG YT, LIAO CH, et al. *In vitro* activities of tigecycline against clinical isolates of Aeromonas, Vibrio, and *Salmonella* species in Taiwan [J]. Antimicrobial Agents and Chemotherapy, 2008, 52(7): 2677 - 2679.

[62] YEN MH, HUANG YC, CHIU CH, et al. Duration of antimicrobial therapy for non - typhoid *Salmonella* bacteremia in healthy children [J]. Journal of Microbiology, Immunology, and Infection, 2002, 35(2): 94 - 98.

[63] TSAI MH, HUANG YC, CHIU CH, et al. Nontyphoidal *Salmonella* bacteremia in previously healthy children: analysis of 199 episodes [J]. The Pediatric Infectious Disease Journal, 2007, 26(10): 909 - 913.

（收稿日期：2024 - 03 - 11；修回日期：2024 - 06 - 14）