

新生儿败血症的临床管理进展

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[摘要] 新生儿败血症是新生儿各类合并症和不良预后的重要原因。国内外新生儿败血症的疾病负担仍较为严重。产时抗生素预防策略、早发型败血症风险计算器的应用和新生儿病房的质量改进等管理方案均有利于减轻新生儿败血症的疾病负担。该文就新生儿败血症的流行病学、危险因素和临床管理进展进行综述。

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[关键词] 新生儿败血症; 产时抗生素预防; 风险计算器; 质量改进; 管理

Advances in clinical management of neonatal sepsis

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Abstract: Neonatal sepsis, as a significant cause of various complications and adverse outcomes in neonates, remains a serious health burden both domestically and internationally. Strategies such as antibiotic prophylaxis during delivery, the utilization of early-onset sepsis risk calculators, and quality improvement initiatives in neonatal wards are beneficial in alleviating the disease burden of neonatal sepsis. This paper provides a review of the epidemiology, risk factors, and recent advances in clinical management of neonatal sepsis.

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Key words: Neonatal sepsis; Intrapartum antibiotic prophylaxis; Risk calculator; Quality improvement; Management

在全球范围内, 每年有约 260 万新生儿死亡, 其中早产、感染和产时相关疾病是主要原因。新生儿期的死亡相关因素中, 有 15% 来源于新生儿败血症^[1]。根据 2018 年一项关于新生儿败血症全球负担的系统综述报告, 新生儿败血症基于出生人口的发生率估计为 2 202/100 000 活产婴儿, 病死率在 11% 和 19% 之间^[2]。亚洲范围内, 新生儿的早发感染由多种不同的病原体引起, B 族链球菌 group B *Streptococcus*, GBS) 感染是早发型败血症 (early-onset sepsis, EOS) 的最常见原因。同时, 多重耐药菌的医院获得性感染在资源较匮乏的亚洲国家很常见, 病原菌以革兰氏阴性菌为主, 病原菌种类和病死率与发达国家相似^[3]。

我国新生儿败血症的血培养阳性率较高, 病死率的城乡差异明显^[4]。病原菌类型持续以凝固酶阴性葡萄球菌为主^[5]。需要全面有效的基于证据的监测策略和恰当的抗生素治疗方案, 以应对越来越多的多重耐药革兰氏阴性菌的出现^[6]。本文对新生儿败血症的流行病学、危险因素及临床管理等研究进展进行综述, 为我国新生儿败血症的诊治提供参考。

1 流行病学

英国于 2004 年建立了全国性的新生儿感染监测网, 以收集和存储新生儿败血症的病原菌及抗生素耐药模式的相关信息^[7]。该监测网 2017 年的

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报告显示新生儿败血症的发生率为6.1/1 000活产婴儿或48.8/1 000入院人数,其中EOS发生率为0.7/1 000活产婴儿或5.6/1 000入院人数;晚发型败血症(late-onset sepsis, LOS)的发生率为2.2/1 000活产婴儿或17.9/1 000入院人数;2005—2014年EOS和LOS的发生率均有显著减少的趋势^[7]。在德国,新生儿败血症的发生率为1 006/100 000活产婴儿^[8]。其他发达国家,如美国、加拿大和澳洲等国家也对新生儿败血症尤其是EOS作了全国性的数据监测和流行病学报告^[9-11]。

有研究报告了2008年和2012年中国、马来西亚、泰国等亚洲国家新生儿败血症的发生情况,研究表明,这些亚洲国家LOS的发生率显著高于西方发达国家^[3, 12]。目前我国尚缺乏全国性的新生儿败血症流行病学调查数据报告。我国华南地区于2019年报告了新生儿败血症的发生率为2.76/1 000活产婴儿,其中EOS的发生率为0.78/1 000活产婴儿,LOS的发生率为2.13/1 000活产婴儿^[13]。另外,有研究统计了我国西部地区1990—2014年入院新生儿发生新生儿败血症的变化趋势,结果显示EOS的发生率有减少趋势,而LOS的发生率无明显增多或减少趋势^[14]。

2 危险因素

母孕期因素是新生儿败血症的重要病因。研究表明,胎龄、母亲GBS感染状态、胎膜早破持续时间、产时最高体温、产时抗生素预防(intrapartum antibiotic prophylaxis, IAP)等因素与新生儿败血症,尤其是EOS高度相关^[15]。母孕期的疾病状态,包括妊娠期感染或病原菌定植都可能加重新生儿败血症的发生风险^[16-17]。母亲发生绒毛膜羊膜炎与新生儿EOS和LOS均有一定的相关性,其可导致新生儿EOS的发生,在其中一些新生儿中可表现为无症状;也可通过调节新生儿出生后免疫状态成为LOS的保护因素^[18-20]。研究表明,通过特殊人群,如超早产儿在围产期的临床特征可确定EOS发生的保护因素,有助于风险分层和减少经验性抗生素的不合理应用^[21]。

院内因素同样是新生儿败血症,尤其是LOS发生的重要原因。研究表明,肠外营养、抗生素联用和外周中心静脉导管置管是新生儿重症监护病房新生儿发生败血症的高危因素^[16, 22]。在极低出生体重儿中,机械通气、喂养不耐受、抗生素

联用、抗生素使用时间长是发生LOS的高危因素^[23]。置管相关感染是新生儿LOS的重要病因,我国脐静脉置管相关败血症发生率为9.5%或13.6/1 000置管日^[24]。研究发现,具体的置管类型与极早产儿置管相关感染发生率关系并不密切^[25]。当存在如置管相关感染、呼吸机相关肺炎、脑膜炎、新生儿坏死性小肠结肠炎等明确感染源时,败血症相关并发症或死亡风险可显著增加^[26]。

3 管理

3.1 IAP策略

IAP策略是新生儿败血症的重要管理策略之一,通过对产妇产时静脉给予抗生素,降低病原菌的垂直传播风险,以减少新生儿败血症的发生^[27]。GBS感染是全球新生儿发生EOS的最常见原因,IAP策略是目前预防围产期早发型GBS感染唯一有效的策略。美国儿科学会与美国妇产科学院合作,于2019年推出最新指南,重申普及产前微生物学检测来评估母孕期GBS定植情况的重要性,并加强IAP策略的有效管理^[27]。这是自1996年美国疾病预防控制中心首次推荐通过IAP策略预防新生儿早发型GBS感染,2002年及2010年支持孕妇GBS筛查以来的又一次更新。郭九叶等^[28]对该指南进行了摘译,以便在我国的推广和临床诊疗指导。目前,IAP策略的有效性在持续评估中^[29-31]。在美国实施IAP策略的2006—2015年间,新生儿早发型GBS感染的发生率显著降低^[31]。

我国母孕期GBS定植比例较高,且地域分布差异明显,在华南地区可高至14.52%^[32]。既往国内研究也证实,对孕妇开展GBS筛查和充分的IAP策略可有效降低新生儿EOS的发生率,尤其是早发型GBS病的发生率^[33-34]。2021年我国推出首部预防围产期GBS病的专家共识,包含了妊娠期GBS筛查方案、围产期抗生素使用方案及GBS菌尿的处理方法^[35]。同期,中国妇幼保健协会新生儿保健专业委员会及中国医师协会新生儿科医师分会共同推出了母婴同室早发感染高危新生儿临床管理专家共识,对EOS高危新生儿的母婴同室和新生儿科管理作进一步规范^[36]。

3.2 EOS风险计算器

2011年,Puopolo等^[15]基于美国1993—2007年608 014例活产婴儿出生队列围产期临床数据,筛选出与新生儿EOS相关的母亲来源的高危因素,

构建了一个EOS多因素预测模型,其表现好于同时期其他算法模型。在此基础上,2014年Kaiser工作部开发出一个适用于胎龄 ≥ 34 周新生儿EOS预测算法,结合当地EOS发生率、母亲来源的危险因素和新生儿临床表现,以将新生儿管理方法分层为经验性应用抗生素、临床观察和评估、进一步观察三类,指导血培养标本采集和经验性抗生素治疗^[37]。该算法以简单实用的计算器方式向全球临床医生免费开放,称为新生儿EOS风险计算器。近十多年来,该方法在全球广泛推广,有效减少了对诊断试验和经验性抗生素治疗的不恰当应用,也未产生明显的不良影响^[38]。美国儿科学会2018年发布的胎龄 ≥ 35 周新生儿疑诊和确诊EOS管理方案中纳入该计算器应用以对相应新生儿进行危险分层^[39]。He等^[40]将该计算器与降钙素原、全血细胞计数和C反应蛋白等实验室指标相结合,发现预测EOS的价值更高。杜秀丽等^[41]总结了EOS风险计算器在新生儿EOS评估中的应用优势。

近年来,国内外多项研究均证实EOS风险计算器的应用有效减少了疑诊EOS新生儿经验性抗生素使用率^[42-44]。Carola等^[45]应用该计算器进一步规范了绒毛膜羊膜炎暴露的新生儿的经验性抗生素用药方案。此外,有研究表明,基于该方案的质量改进措施具备一定的实用价值和经济价值^[46-47]。EOS风险计算器在英国、澳大利亚等发达国家以及包括我国在内的发展中国家均有效开展应用^[40, 48-49]。英国在引入EOS风险计算器时,与本国现有管理方案作比较,并对该计算器的应用作出本土化改良和指导^[50-52]。这对于EOS风险计算器在我国的进一步推广应用有一定的参考价值。

3.3 质量改进

研究表明,通过新生儿重症病房内的质量改进措施,可有效减少新生儿感染的发生,尤其是外周中心静脉导管置管相关性血流感染^[53-55]。Meta分析结果也表明,基于集束化策略的质量改进能降低中心导管相关血流感染的发生率,但是具体的有效措施未明,而集束化策略在全球应用中还未有统一规范^[56]。我国于2015年也开展了全国性的基于证据的质量改进项目研究,内容包括手卫生、抗生素使用、喂养、呼吸机管理、中心静脉管理、感染事件调查、皮肤穿刺等方面^[57]。研究表明,我国的集束化改进措施能有效降低早产儿LOS的发生^[58]。另有研究表明,质量改进项目的开展对改善新生儿预后和病死率有潜在益处^[59]。

4 结语

本文从流行病学、危险因素及临床管理等方面总结了新生儿败血症目前国内外临床研究和应用进展。我国新生儿败血症的临床管理策略仍有欠缺。进一步优化新生儿败血症的临床管理方案,有利于降低新生儿败血症的发生率,改善新生儿的近远期临床结局。

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