

脓毒症患儿抗生素的临床应用

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摘要

脓毒症是一种高发病率和死亡率的疾病, 是儿童入住重症监护病房的主要原因之一, 也是ICU患者死亡的主要原因。脓毒症极大危害了人类的健康, 大大加重了社会的经济负担, 消耗了大量的医疗资源, 也给很多家庭带来了沉重的打击。脓毒症的救治面临着重大的挑战, 及时有效的治疗方式干预有利于降低脓毒症的死亡率, 改善患者远期预后, 具有重大的意义。脓毒症由感染引起, 抗生素是治疗脓毒症的重要措施, 然而, 抗生素的使用有一定的原则, 过早使用抗生素或过多使用高级抗生素易造成超级耐药细菌的产生, 过晚使用抗生素则不利于病人的救治, 可能延误治疗, 加重患者病情, 增加死亡风险。抗生素规范合理的应用对脓毒症的救治至关重要, 需引起临床工作者的高度重视, 现对脓毒症患儿临床抗生素的应用情况做一综述, 为优化临床脓毒症患儿的抗感染治疗方案提供一些参考。

关键词

脓毒症, 儿童, 抗生素, 临床应用

Clinical Application of Antibiotics in Children with Sepsis

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Abstract

Sepsis is a disease with high morbidity and mortality. It is one of the main causes of intensive care

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unit admission in children and the leading cause of death in ICU patients. Sepsis greatly endangers human health, greatly increases the economic burden of society, consumes a lot of medical resources, and also brings a heavy blow to many families. The treatment of sepsis is facing major challenges. Timely and effective treatment intervention is of great significance to reduce the mortality rate of sepsis and improve the long-term prognosis of patients. Sepsis is caused by infection. Therefore, using antibiotics is an important measure for the treatment of sepsis. There are some principles for the use of antibiotics. Too early use of antibiotics or too many advanced antibiotics to be used can easily cause the emergence of drug-resistant bacteria, but too late use of antibiotics is not conducive to the treatment of patients, which may delay treatment, aggravate patients' conditions, and increase the risk of death. The standardized and reasonable use of antibiotics is very important and requires great attention, especially for clinicians. The application of antibiotics in children with sepsis is reviewed to provide some references for optimizing the anti-infective treatment regimen for children with sepsis.

Keywords

Sepsis, Children, Antibiotics, Clinical Application

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1. 脓毒症的定义

脓毒症(Sepsis)是指因感染引起的宿主反应失调导致的危及生命的器官功能障碍,是导致疾病和死亡的重要原因。几十年来,脓毒症的定义和指南不断更新,但仅有部分指南适用于儿童。2005年,首次提出了儿童脓毒症的诊断标准,脓毒症被定义为感染合并全身炎症反应综合征(SIRS),严重脓毒症指脓毒症合并器官功能障碍,脓毒性休克则被定义为脓毒症合并心血管功能障碍[1]。此后,为了尽快识别脓毒症,减少脓毒症患者的死亡率,脓毒症的诊断标准经过不断更新,最新的指南发表于2024年,推出了Phoenix脓毒症诊断标准,包括呼吸、心血管、神经和凝血功能障碍的标准,指出儿童疑似感染且Phoenix评分 ≥ 2 分诊断为脓毒症,满足脓毒症的诊断标准且心血管评分 ≥ 1 分即诊断为脓毒性休克[2]。新标准通过大规模的国际数据库和调查、系统文献综述和荟萃分析以及改良的德尔菲共识法共同推导和验证,在全球范围内均适用,能更可靠地识别脓毒症患儿,改善脓毒症预后。

2. 临床常用抗生素的分类及作用机制

抗生素是重症医学科最常使用的药物,在脓毒症及脓毒性休克的救治中发挥着重要的作用,其种类多样,每种抗生素的作用机制及适应症各不相同。临床上常将抗生素分为 β -内酰胺类、氨基糖苷类、喹诺酮类、大环内酯类、四环素类、林可霉素类、糖肽类等。其中 β -内酰胺类又分为青霉素类、头孢类、碳青霉烯类,属于时间依赖性抗生素,抗菌后效应持续时间短,需一天内多次给药。氨基糖苷类抗生素对革兰阴性杆菌作用强大,对革兰阴性球菌、厌氧菌作用差,有剂量依赖性,抗菌后效应持续时间长,使用时需注意其耳毒性、肾毒性的副作用。喹诺酮类抗生素对各种各样的细菌,包括革兰阳性菌、革兰阴性菌,甚至衣原体、支原体、结核菌均有作用,最适用于肠道感染,临床上以左氧氟沙星最为常用。大环内酯类对各种细菌均有作用并偏向于革兰阳性菌,其亮点是对支原体、衣原体有效。四环素类常用抗生素有多西环素和米诺环素,国内用于社区获得性肺炎和非淋菌性尿道炎的治疗,近年来由于耐药肺炎支

原体的大流行,使得多西环素在儿科患者中的使用率大大提高[3]。林可霉素类对 G⁺菌作用强大,对厌氧菌效果好。糖肽类抗生素主要代表药物为万古霉素、替考拉宁,是治疗耐甲氧西林葡萄球菌、肠球菌等多重耐药 G⁺球菌的首选药。

从不同的角度出发,抗生素也有其他不同的分类方法。从药代动力学和药效学出发,抗生素可分为时间依赖性抗生素和浓度依赖性抗生素两大类[4],时间依赖性抗生素的抗菌效应与临床疗效主要与细菌接触时间密切相关,一般推荐日剂量分多次给药或延长滴注时间的给药方案,抗菌后效应持续时间短,头孢类、碳青霉烯类、糖肽类等属于此类,浓度依赖性抗生素对致病菌的杀菌效应和临床疗效取决于血药峰浓度,一般推荐日剂量单次给药方案,氨基糖苷类、氟喹诺酮类抗生素属于此类。从抗生素的作用对象来分,分为抗菌药物、抗病毒药物、抗真菌药物等。从作用效果来分,抗菌药物又可分为抑菌类抗生素和杀菌类抗生素。

不同的抗生素在病原体形成的不同阶段发挥着作用,即抗生素的作用机制不同,包括阻断细胞壁合成、损伤细胞膜影响通透性、阻断核糖体蛋白质合成、影响叶酸代谢、阻断 RNA 或 DNA 合成。

3. 抗生素在脓毒症患儿中的应用

3.1. 合理应用抗生素的必要性

早期识别感染,尽早开始有效的抗感染治疗是抢救脓毒性休克患者的关键步骤,有利于降低脓毒症患者的死亡率,缩短患者的住院时间,减少远期并发症,改善患者预后[5],但很多时候,未受到致病菌侵袭的患者也接受了抗菌药物的治疗,导致了抗生素的滥用[6]。感染的成功控制是脓毒症和脓毒性休克复苏的关键因素,抗感染治疗是脓毒症治疗的核心组成部分,同时,为了避免超级耐药菌的产生及药物副作用的影响,抗生素的合理使用至关重要。

3.2. 抗生素使用的原则

使用抗生素时,最理想的状态便是在保证临床疗效的前提下,尽可能地缩短疗程、减少副作用。2020年,有学者提出了抗生素治疗的“5Ds”原则[7],即“决定(Decision)、药物(Drug)、剂量(Dose)、降阶梯(De-escalation)、疗程(Duration)”。然而,影响抗生素使用的因素多种多样,即使已有不少指南对抗生素的使用原则提出了指导和建议,在临床具体应用时依旧很难做到统一标准。感染的严重程度、感染部位、病原体的特性均会影响到抗生素的选择及疗程。

3.3. 抗生素应用的时机

抗生素的应用时机存在争议,针对儿童脓毒症何时开始进行抗生素治疗的研究相对较少,但已有大量的相关研究在成人中开展。大多数学者认为在脓毒症诊断明确时,尽快使用抗生素可以降低住院病死率、改善患者预后[8] [9],有研究表明,抗生素每延迟使用 1 小时,患者的死亡风险将会显著增加[10]-[13]。两项针对儿童的回顾性观察性研究分析也表明,延迟使用抗生素会增加脓毒症患儿的死亡率和器官功能障碍持续时间,每延迟一小时,死亡风险都会增加,尽管与小于 3 小时相比,只有当抗生素给药时间大于 3 小时,死亡率增加才达到显著差异[14] [15]。但仍有部分学者对此持反对意见,认为抗生素早期使用与脓症患者病死率降低并不相关[16] [17],且早期不合理的抗生素治疗,可以造成微生物菌群的变化及耐药性的增强,引起不必要的费用及严重的药物不良反应等[6] [18]。基于现有儿童临床研究的直接证据,并结合成人研究所得出的结论的间接证据,2020 年儿童脓毒症指南中建议在不显著延迟抗菌治疗的前提下,应尽可能采集血培养及其他生物标本以识别病原体,为后续脓毒症的治疗提供依据。同时,该指南对脓毒症及脓毒性休克的患儿抗生素的应用时机做出了不同的推荐,即对于脓毒性休克患儿,建

议在发现后 1 小时内尽快开始抗感染治疗(强烈推荐), 对于脓毒症合并相关器官功能障碍但无休克或诊断尚不明确儿童, 建议在进行适当评估后, 在识别后 3 小时内尽快开始抗感染治疗(推荐性较弱) [19]。

3.4. 抗生素的降阶梯治疗

抗生素的使用可分为两个阶段, 初始为经验性治疗阶段, 在 24~48 小时以后, 需对使用抗生素的合理性和有效性进行动态评估, 调整抗生素的使用, 及时进行抗菌药物降阶梯治疗(antibiotic de-escalation, ADE), 此为抗感染治疗的第二阶段。2020 年欧洲重症监护医学学会(ESICM)与欧洲临床微生物学和感染病学学会(ESCMID)危重病患者研究组(ESGCIP)对于 ADE 给出了专业的循证指导[20]: 第一, 推荐建立在确定的培养结果和抗菌谱可用的 24 小时内, 进行抗菌素的重新评估。第二, 除了难以治疗的病原菌感染外, 对所有细菌性病原体感染, 进行降阶梯的推荐。第三, 建议对培养阴性的危重症患者, 考虑交替进行非感染性诊断, 并停止全部或者部分抗生素治疗。第四, 推荐降阶梯可用于中性粒细胞减少的危重患者。第五, 降阶梯可以适用于所有感染源。2020 年儿童脓毒症指南也提出, 推荐使用一种或多种抗菌药物进行经验性广谱治疗, 以覆盖所有可能的病原体, 一旦病原学结果明确, 立即根据病原体及药敏试验结果更换抗生素, 如未发现病原体, 则根据患儿的临床表现、感染部位、合并症、临床症状是否改善等, 缩小经验性抗感染治疗的范围或停止经验性抗感染治疗[19]。

儿童脓毒症的抗生素经验性治疗阶段, 应结合年龄组、基础疾病和当地流行病学情况进行选用, 初始使用广谱抗生素, 一旦确定了病原体, 应针对病原体调整有效的抗生素[21]。例如: 在初始抗感染治疗阶段, 考虑革兰氏阴性菌感染的脓毒症患儿, 首选哌拉西林他唑巴坦或三代以上头孢菌素, 若有重症或耐药高风险患者, 则使用碳青霉烯类抗菌药物; 对于革兰氏阳性菌感染可能性大的患儿, 若耐甲氧西林金黄色葡萄球菌(MRSA)感染不排除或感染严重, 则使用万古霉素或利奈唑胺; 对于有严重基础疾病或胸腔感染严重, 考虑合并厌氧菌感染的患儿, 可加用甲硝唑。若后续病原体结果明确或临床症状好转, 则开始降阶梯治疗。对于检出革兰氏阴性菌者, 碳青霉烯类抗菌药物可降阶为三代头孢菌素或哌拉西林他唑巴坦; 对于甲氧西林敏感的金黄色葡萄球菌(MSSA), 停用万古霉素, 改用苯唑西林或一代头孢菌素; 明确检出病原体为敏感肺炎链球菌者, 可改为青霉素或阿莫西林。若病原学未明确但临床症状改善者, 也应及时进行降阶梯治疗, 无 MRSA 风险者停用万古霉素/利奈唑胺, 无厌氧菌证据者停用甲硝唑, 将广谱抗生素改为抗菌谱更窄的抗生素, 多种抗菌药物联合抗感染者减少抗菌药物的种类。对于免疫功能低下或医院获得性脓毒症, 经验性抗感染治疗应选用第三代或更高代头孢菌素(如头孢吡肟)、广谱碳青霉烯类(如美罗培南、亚胺培南)、青霉素/ β -内酰胺酶抑制剂复合制剂(如哌拉西林/他唑巴坦) [22], 待病情好转后可降阶为二代头孢、阿莫西林克拉维酸钾等。

由于当存在病原体时, 大多数病原学检查结果在标本采集后 24~36 小时内可报告, 因此应在开始抗感染治疗不超过 48 小时重新评估经验性治疗的合理性。如果未发现病原体, 且认为不太可能发生细菌或真菌感染, 临床医生应停止经验性抗菌治疗, 以减少不必要的抗生素或抗真菌药物的使用, 若发现明确的病原体感染, 则针对性地使用抗生素。因重症医学病房中患者病情重, 常合并各种基础疾病, 病情复杂, 耐药菌检出率高, ADE 在 ICU 患者中的应用受到限制[23], 但一项针对脓毒症及脓毒性休克患者的多中心前瞻性观察性队列研究仍表明[24], 即使在多重耐药菌检出率较高的重症医学病房, ADE 也是有必要的, 可能与较低的死亡率有关。

3.5. 儿童脓毒症抗生素的使用困境

抗生素在脓毒症的治疗中发挥着不可替代的作用, 抗生素的使用可以大大降低脓毒症患儿的死亡率。然而, 抗生素在临床中的应用并不规范, ADE 往往不能有效实施, 也导致了抗生素的滥用, 从而增加了

病原的耐药性。

入住 PICU 的脓毒症患者往往由于疾病严重与复杂, 大多数接受了经验性抗感染治疗, 但研究发现多达 50% 的治疗可能是不恰当的[25]。虽然 ADE 被推荐为一种抗菌药物管理策略, 但由于患儿年龄小、病情变化快、病情重、炎症指标持续增高等, ADE 对脓毒症患者预后的影响存在争议, 因此临床应用情况不理想[26][27]。有研究表明, 儿童脓毒症能得到充分的经验性抗生素治疗, 但 ADE 的实施远远不足。因此, 临床医生应提高 ADE 的理念和意识, 医院也应开展相关培训, 建立督查小组, 加强临床工作中抗生素的合理使用。

不恰当使用抗生素加剧了细菌耐药的发生发展。既往一项研究表明, 虽然随着社会的经济发展, 抗生素的使用增多, 但每年仍有 100 多万患有肺炎和脓毒症的儿童因未能得到救治而死亡[28]。与此同时, 由于抗生素的不合理使用, 细菌耐药率越来越高, 抗生素有效性降低, 使得全球都面临着新的挑战[22][29]。有数据表明, 50% 以上引起新生儿感染的病原体对氨苄西林和庆大霉素耐药[30][31], 同时, 随着超广谱 β -内酰胺酶在大肠杆菌中的产生, 超广谱头孢菌素的应用也受到了限制[32], 碳青霉烯类药物, 如厄他培南、美罗培南和亚胺培南等, 在临床上的应用有所增加, 成为儿童感染侵袭性超广谱 β -内酰胺酶细菌的首选抗菌药物[33]。然而, 碳青霉烯类抗生素应用增加的同时, 碳青霉烯类抗菌药物的耐药率也越来越高, 已成为全球公共卫生问题[34][35]。多粘菌素类抗生素和替加环素是成人多重耐药革兰氏阴性菌的重要抗感染药物, 但因粘菌素的肾毒性[21], 使其在儿童中的应用受到限制, 替加环素也因其可能导致死亡率的增加, 不推荐常规应用于儿童。

4. 结语

脓毒症是全世界儿童死亡的一个主要原因[36][37], 抗生素的使用是脓毒症治疗的关键环节, 识别脓毒症之后, 应尽快给予有效的抗生素治疗, 降低脓毒症患者的死亡风险[38][39], 然而, 在抗生素使用的第一个环节, 即经验性治疗环节, 由于病原体尚不明确, 容易造成抗生素的非必要使用[6], 因此, 临床医生应提升自己的专业水平, 结合患者的病史特点, 充分利用初步检验检查结果, 做出尽可能准确的判断, 减少抗生素不合理使用带来的不良后果。ADE 是临床抗生素应用与管理的重要组成部分。缩短经验性抗生素的治疗时间, 及时进行降阶梯治疗, 有利于降低脓毒症患者的死亡率[40]-[42]。抗生素的不合理使用加剧了细菌耐药性的发生发展, 使得可供选择的有效抗菌药物越来越少, 脓毒症患儿的抗感染治疗面临着重大的困难和挑战。同时, 由于儿童多器官、系统发育不完善, 各种药物副作用对儿童的损害更加明显, 很多药物缺乏在儿科患者中的应用经验, 因此, 儿童用药需更为谨慎。在保证医疗安全的前提下, 有必要在儿科人群中加大开展关于抗生素应用的高质量临床试验的力度, 以探索和明确儿童感染的最佳治疗方案和药物剂量。

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