

认识儿童急性肾损伤

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[摘要] 急性肾损伤 (acute kidney injury, AKI) 以可逆性的血肌酐和尿素氮升高以及肾脏对水、电解质调节失衡为临床特征。AKI 在儿童的发病率逐年升高, 住院儿童及成人 AKI 发病率的增加与其病死率密切相关。继续依赖血肌酐和尿量去诊断 AKI 导致不能早期提供有效的治疗和支持性的干预措施去阻止和缓解 AKI 的发生。最近 10 年实验研究重点在发现和验证在肾功能改变之前识别 AKI 及有助于鉴别诊断的新的生物标志物。

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[关键词] 急性肾损伤; 血肌酐; 儿童

Recognizing pediatric acute kidney injury

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Abstract: Acute kidney injury (AKI) is characterized by a reversible increase in blood concentration of creatinine and nitrogenous waste products and by the inability of the kidney to regulate fluid and electrolyte homeostasis appropriately. AKI in hospitalized patients is independently associated with increased morbidity and mortality in pediatric and adult populations. Continued reliance on serum creatinine and urine output for the diagnosis of AKI has resulted in an inability to provide successful therapeutic and supportive interventions to prevent and mitigate AKI. Research efforts over the last decade have focused on the discovery and validation of novel biomarkers to detect AKI prior to a change in kidney function and to make a differential diagnosis of AKI.

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Key words: Acute kidney injury; Serum creatinine; Child

1951 年 Homer W Smith 提出急性肾衰竭 (acute renal failure, ARF) 以来, ARF 的定义一直没有得到统一, 至少有大于 30 种不同 ARF 的定义, 使 ARF 临床研究结果难以比较, 也难以得出研究的结论, 且血肌酐 (Scr) 的微小变化, 其预后也不一样。所以, 急性透析质量指导组 (Acute Dialysis Quality Initiative Group, ADQI) 提出急性肾损伤 (acute kidney injury, AKI) 的定义, 其较 ARF 包括范围更广, 概念明确了从早期轻度到后期严重程度, 并通过标准验证了不管是否存在肾衰竭, Scr 变化都与预后有关^[1]。而且 “injury” 在病理生理表述上较 “failure” 更准确, “kidney” 较 “renal” 更好理解。

1 AKI 定义及分期标准

ADQI 将 AKI 分为 5 期^[1], 简称 RIFLE, 即风险期 (risk of renal dysfunction, R), 损伤期 (injury to the kidney, I), 衰竭期 (failure of kidney function, F), 功能丧失期 (loss of kidney function, L) 和终末期肾脏病期 (end stage renal disease, E)。前 3 个为严重程度级别, 后 2 个为预后级别。2005 年急性肾损伤网络 (Acute Kidney Injury Network, AKIN) 在荷兰阿姆斯特丹制定了新的 AKI 共识, 把 AKI 定义为: 肾脏功能或结构方面的异常 (包括血、尿、组织检测或影像学方面的肾损伤标志物异常), 时限不超过 3 个月。同时制定了相应

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的诊断标准：肾功能在48 h内突然减退，表现为Scr升高，绝对值 $\geq 26.4 \text{ mol/L}$ ，或Scr较基础值升高 $\geq 50\%$ ；或尿量减少 $<0.5 \text{ mL/(kg}\cdot\text{h)}$ ，时间超过6 h。（1）风险期：Scr是基线值的1.5倍，或肾小球滤过率（GFR）下降 $>25\%$ ，尿量 $<0.5 \text{ mL/(kg}\cdot\text{h)}$ ，持续6 h；（2）损伤期：Scr是基线值的2倍，或GFR下降 $>50\%$ ，尿量 $<0.5 \text{ mL/(kg}\cdot\text{h)}$ ，持续12 h；（3）衰竭期：Scr是基线值的3倍，或Scr $>4 \text{ mg/dL}$ （ $>354 \text{ mol/L}$ ）伴急性升高 $>0.5 \text{ mg/dL}$ （ $>44 \text{ mol/L}$ ），或GFR下降 $>75\%$ ，尿量 $<0.3 \text{ mL/(kg}\cdot\text{h)}$ 持续24 h或无尿12 h；（4）功能丧失期：持续急性肾衰竭=完全丧失肾功能 >4 周；（5）终末期肾脏病期：终末期肾脏病 >3 个月。

RIFLE分期可在成人AKI的病程、费用、发病率及病死率上进行独立的预测。Bell等^[2]报道30 d内AKI风险期、损伤期、衰竭期病死率分别为23.5%、22.0%及57.9%。Maccariello等^[3]的报道则分别为72%、79%及76%。目前所有超过200000病例研究表明，RIFLE分级越重，病死率越高，住院及ICU住院时间越长，肾功能恢复越低（病人出院时Scr更高）^[4]。Akcan-Arikan等^[5]采用改良RIFLE分期标准并在危重患儿AKI中的应用发现：150例病人中，123例在第一周发生AKI（82%），27例对照组未发生AKI，RIFLE第一阶段的平均发生时间为入住ICU的 $3.3 \pm 3.1 \text{ d}$ ，11例透析，24例死亡。入住ICU第一周末发生AKI的病人发生肾损伤和衰竭的可能性小。

2 RIFLE分期存在的问题

Scr作为肾损伤的指标实际上反映的是GFR，肾前性肾衰竭GFR下降、Scr上升、尿量减少，但是早期并无肾损伤，Scr作为晚期标志物临床应用让AKI的诊断干预延迟，导致AKI的预后不理想。且Scr随年龄、性别、饮食、肌肉群、疾病不同而改变（横纹肌溶解上升，神经肌肉病下降）。药物也影响Scr分泌，如甲氧苄氨嘧啶、甲氧咪唑可使Scr短暂可逆性升高。糖尿病酮症酸中毒Jaffe反应、头孢西丁、氟胞嘧啶、胆红素的干扰可出现Scr升高的假象。而尿量下降也不一定意味损伤，可能为正常病理生理反应，因为尿量的影响因素很多，如利尿剂可影响尿量，泌尿道的梗阻

可出现无尿的现象，尿量和Scr水平并不平行。而且Scr及GFR的基线值在临床病人中时常缺乏，从而使RIFLE分期出现困难。

3 早期生物学标志的研究

早期生物学标志诊断优势主要体现在GFR改变之前出现的肾小管损伤指标，为分子和细胞水平上损伤的信号。理想的生物学标志其可能在识别AKI病因（缺血、中毒、败血症）、判断临床亚型（肾前性、肾性、肾后性）、鉴别AKI的疾病并及时干预，从而出现更好预后有重大意义，而且在反映疾病严重性、监测进展、指导预后中有重大的价值。目前有4种AKI生物学标记已在不同临床试验验证，包括中性粒细胞明胶酶相关脂质运载蛋白（NGAL）、白介素-18（IL-18）、肾损伤分子-1（KIM-1）、肝脂肪酸结合蛋白（L-FABP）^[6]。在体外循环AKI的研究中发现：在NGAL升高的36~48 h中Scr未升高，所以NGAL监测提供一个以前没有发现的潜在治疗时机来干预阻止减轻AKI。IL-18、KIM-1及L-FABP在体外循环中研究（TRIBE-AKI）发现：NGAL、IL-18显示了对AKI稳定的预测（较单纯临床风险因子），在体外循环发展为AKI过程中，2 h NGAL上升，IL-18和L-FABP 6 h上升，KIM-1在12 h后上升。而且尿中的上述生物学标记较临床风险因子更能提高AKI的预测力，临床上合并使用在AKI的不同时段表现更有优势，更准确^[7-13]。另外，在儿童重症病人发展AKI中，NGAL上升较Scr提前2 d，非败血症AKI中IL-18上升较Scr提前2 d。成人ICU最近数据显示：入住ICU 2 d内NGAL、IL-18及Cystatin C在预测发生评估AKI的不同阶段不同时间点中也有一定的合理性^[14]。

4 AKI的预防

已有两个研究^[15-16]显示AKI最重要原因为血容量不足，为可预防的。AKI的预防对病死率的影响较其他治疗方法显得更为重要。KDIGO推荐如非出血性休克，建议使用等张的晶体液而不用胶体液（白蛋白或淀粉）来扩张具有AKI风险或患AKI病人的血管内容积，对于血管收缩性休克病人，

推荐使用血管加压素加液体的治疗方法。KIDGO推荐重症病人使用胰岛素疗法,血浆葡萄糖控制在110~149 mg/d (6.1~8.3 mmol/L),建议任何阶段的AKI病人,总能量摄入为20~30 kcal/(kg·d),不建议为防止或推迟肾替代疗法而限制蛋白摄入,建议在非分解代谢的、不需要透析的AKI病人,摄入蛋白0.8~1.0 g/(kg·d),肾替代疗法的AKI病人1.0~1.5 g/(kg·d),持续肾替代疗法和高分解代谢病人,蛋白摄入最大至1.7 g/(kg·d)^[17]。

腺苷为强血管收缩剂,缺血中由ATP分解代谢释放;茶碱结合腺苷受体是其保护急性肾损伤的可能机制,严重窒息新生儿每小时内静脉予茶碱,可改善液体平衡及肌酐清除,降低Scr水平,严重窒息新生儿KDIGO推荐给予一剂氨茶碱治疗。但有研究发现使用茶碱组新生儿持续肺高压的发生率更高,需进一步研究其可能的副作用^[17-20]。

AKI过程中少尿转变成无尿并未改变AKI的进程,RCT(成人AKI透析者)研究表明,虽然利尿剂呋塞米较安慰剂组显著缩短病程,但最终透析方式、时间及病人的成活率并无差别^[17]。

“肾性剂量”的多巴胺[0.5 μg/(kg·min)至3~5 μg/(kg·min)]可提高缺血肾的灌注,但没有明确研究证明可减少AKI透析需要及提高生存时间^[21-25]。非诺多泮是强烈、短效、选择性多巴胺受体1拮抗剂,可减轻血管收缩,增加肾血流,可减少AKI发生率,减少肾替代治疗需要,减少ICU入住时间,减少各种原因AKI病死率^[26]。但也有临床观察未发现非诺多泮有预防AKI作用,由于非诺多泮降低血压的不良反应,因而有加重AKI的潜在风险,非诺多泮的临床疗效有待进一步证实,KDIGO不建议用非诺多泮治疗AKI^[17]。

动物模型显示胰岛素样生长因子-1(IGF-1)、上皮生长因子、肝细胞生长因子可促进肾功能修复,减轻病理程度及减少病死率,氧自由基清除剂,分子氮及抗粘附分子也可减轻损伤程度^[27-28],多能间充质干细胞(mesenchymal stem cells, MSCs)也可能促进AKI的损失修复^[29]。但是临床研究结果不尽人意,包括心房肽(anaritide)及IGF-1等的研究。分析可能与实验以肾功能改变来决定治疗时机选择较晚有关。推测如果采用比Scr更敏感的生物标志来评估损伤以决定治疗时机可能对研究结果会有不同的影响^[30-31]。

5 AKI预后

AKI预后与病因有关。多系统衰竭病例较肾脏疾病(溶血尿毒综合症、急进性肾小球肾炎、急性肾小管坏死)病死率高,肾毒性AKI及缺血缺氧AKI常常肾功能能够恢复。成人研究发现了AKI转为慢性肾脏疾病的问题。肾脏生长期发生AKI可减少肾单位数目导致肾小球肥大,残留肾单位高滤过导致残留肾单位肾小球硬化,肾单位丢失是发生晚期肾衰竭高风险重要因素。新生儿期皮质坏死(即使肾功能已恢复)、严重过敏性紫癜及溶血尿毒综合症是发生晚期肾脏合并症的高风险因素,而且新生儿期的AKI也与以后肾脏疾病发生有关,所以目前已将AKI作为慢性肾脏疾病的独立预测因素之一^[32-37]。

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