

降钙素原 (PCT) 急诊临床应用的专家共识

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感染性疾病是急诊科常见的疾病之一,由感染引起的全身炎症反应综合征是脓毒症最根本的病理生理学改变。由于全身炎症反应的复杂性,至今尚无理想的诊断、分层、预后工具和效果显著的治疗方案。已有不少研究证实,脓毒症早期的病理生理改变是功能性的、可逆的。因此,早期准确地诊断脓毒症并监测是改善预后的决定性因素之一。降钙素原 (procalcitonin, PCT) 与感染和脓毒症的相关性很好,经过近 20 年的研究和实践,已经被推荐用于细菌感染性脓毒症的诊断、分层、治疗监测和预后评估。

1 PCT 简介

1.1 PCT 主要的生物学效应

PCT 的生物学效应目前尚无明确的结论,主要的生物学效应有:次级炎症因子的作用、趋化因子的作用、抗炎和保护作用^[1-5]。

1.2 PCT 的检测方法和稳定性

目前 PCT 可通过半定量和定量方法检测。半定量方法有胶体金标志检验,定量方法包括放射免疫分析法、免疫荧光法、双抗夹心免疫化学发光法、酶免法等。

PCT 在血样中非常稳定,采血后在室温下放置 24 h, PCT 质量浓度仅下降 12% 左右,如果在 4℃ 保存仅下降 6%。冰冻、抗凝剂、血清或者血浆、动脉血或者静脉血对检测结果的影响均微乎其微。如果需要长时间存放后检测,则需要低温或者冰冻保存血样^[6]。

1.3 PCT 的正常值及参考范围

健康人的血浆 PCT 质量浓度低于 0.05 ng/ml。老年人、慢性病患者、以及不足 10% 的健康人血浆 PCT 质量浓度高于 0.05 ng/ml,最高可达 0.1 ng/ml,但一般不超过 0.3 ng/ml。脓症患者 PCT 的诊断界值为超过 0.5 ng/ml,严重脓毒症和脓毒性休克患者 PCT 质量浓度波动在 5~500 ng/ml 之间。极少数严重

感染患者血浆 PCT 水平超过 1000 ng/ml。

PCT 质量浓度的临床意义和处置建议见表 1。

表 1 对于 PCT 结果判读的建议

PCT 质量浓度 (ng/ml)	临床意义	处置建议
<0.05	正常值	—
<0.5	无或轻度全身炎症反应。可能为局部炎症或局部感染。	建议查找感染或者其他导致 PCT 增高的病因。
0.5~2	中度全身炎症反应。可能存在感染,也可能是其他情况,如严重创伤、大型手术、心源性休克。	建议查找可能的感染因素。如果发现感染,建议 6~24 h 后复查 PCT。
2~10	很可能为脓毒症、严重脓毒症或脓毒性休克。具有高度器官功能障碍风险。	建议每日复查 PCT。如果 PCT 持续高水平 (>4 d): 重新考虑脓毒症治疗方案。
≥10	几乎均为严重细菌性脓毒症或脓毒性休克。常伴有器官功能衰竭,具有高度死亡风险。	建议每日检测 PCT 以评价治疗效果。

注: PCT 水平必须结合临床情况进行判读。应避免脱离患者具体病情而进行判读,并应考虑假阳性和假阴性的可能性

1.4 导致 PCT 升高的常见疾病

导致 PCT 升高的常见疾病见表 2。

表 2 导致 PCT 异常的常见疾病

导致 PCT 异常的常见疾病
细菌感染导致的全身炎症反应
手术后
严重创伤 (多发伤)
严重烧伤
持续性心源性休克
严重的灌注不足、MODS、重症胰腺炎
严重的肾功能不全和肾移植后
严重的肝硬变、或急/慢性病毒性肝炎
新生儿出生的最初几天
中暑
真菌感染
某些自身免疫性疾病
肿瘤晚期、副癌综合征
横纹肌溶解症
持续心肺复苏后
药物因素: 使用抗淋巴细胞球蛋白、抗 CD3 或鸟氨酸-酮酸转氨酶抗体、大剂量的促炎因子后

2 PCT 水平监测在急诊常见感染性疾病的临床应用建议

2.1 细菌感染

2.1.1 呼吸系统感染 引起肺炎的病原微生物种类较多,包括病毒、细菌、真菌和不典型病原体。因此 PCT 水平在肺炎患者中呈现多样性,主要与病原体的类型、肺炎的严重程度以及全身炎症反应的严重程度有关。

细菌性肺炎患者的 PCT 水平高于病毒、不典型病原体(军团菌除外)和结核菌导致的肺炎。但不是所有的细菌性肺炎患者 PCT 水平都增高,约 50% 的细菌性肺炎患者 PCT < 0.5 ng/ml。28% 的细菌性肺炎患者 PCT < 0.1 ng/ml,因此 PCT 正常或轻度增高不能排除细菌性肺炎^[7-8]。

PCT 水平与肺炎的严重程度呈正相关。低水平 PCT (< 0.1 ng/ml) 提示可能是肺炎较轻、预后较好,或是病毒性肺炎、非典型病原体导致的肺炎,是不使用或停用抗生素的参考指标^[9]。

监测 PCT 的变化趋势可以作为抗生素治疗效果的评估手段,PCT 持续升高或者不降是治疗无效的表现^[10-18]。

在严重社区获得性肺炎(SCAP)、院内获得性肺炎(HAP)以及呼吸机相关性肺炎(VAP)中,PCT 水平与痰细菌培养阳性率、病情的严重程度呈正相关。初始 PCT 水平高并且在治疗过程中持续升高或不降是预后不良的标志。

表 3 呼吸道感染患者 PCT 水平的临床意义和处置建议

PCT 质量浓度 (ng/ml)	临床意义	处置建议
< 0.1	基本没有细菌感染的可能性	强烈建议不使用抗生素
0.1 ~ 0.25	细菌感染的可能性不大	不建议使用抗生素
0.25 ~ 0.5	可能存在需要治疗的细菌感染	建议使用抗生素
> 0.5	很可能存在需要治疗的细菌感染	强烈建议使用抗生素

注:(1)对于入院时已经服用抗生素的患者,PCT < 0.25 ng/ml 建议停用已经使用的抗生素。(2)如果与基线值比较,PCT 质量浓度下降 80% 以上,建议停用抗生素。下降 90%,强烈建议停用抗生素

2.1.2 细菌性心内膜炎 细菌性心内膜炎初期症状没有特异性,但是 PCT 水平可能增高。对于存在相关危险因素(如心脏瓣膜病、瓣膜置换术后、免疫力低下、静脉吸毒等)并出现非特异

性感染症状的患者,如果 PCT 水平增高,需要考虑细菌性心内膜炎的可能^[19]。如果超声心动图(包括经食道超声 TEE)结果正常,应在短期内复查 PCT。

PCT 诊断心内膜炎的最适界值为 2 ~ 3 ng/ml,而排除界值为 0.1 ~ 0.25 ng/ml。

2.1.3 急性细菌性脑膜炎 细菌性脑膜炎的 PCT 通常高于 0.5 ng/ml。病毒性脑膜炎和局灶性感染 PCT 一般不升高。如果以 PCT > 5 ng/ml 作为诊断界值,诊断细菌性脑膜炎的敏感度为 94%,特异性为 100%^[20]。

如果临床疑及脑膜炎并且 PCT 水平增高,建议开始抗生素治疗。如果 PCT 阴性,而其他的证据支持细菌性脑膜炎的诊断,也应开始抗生素治疗。如果连续监测 PCT 持续阴性,并且其他支持细菌性脑膜炎的证据不足,可考虑停用抗生素。

2.1.4 细菌性腹膜炎 研究发现细菌性腹膜炎的血浆 PCT 水平显著增高,局限性腹膜炎(阑尾炎、胆囊炎等)的血浆 PCT 水平仅中度增高或不增高。肝硬化腹水不合并感染的患者 PCT 水平正常,合并感染后血浆和腹水 PCT 水平都明显增高^[21-22]。

2.2 病毒感染

病毒性疾病时 PCT 不增高或仅轻度增高,一般不会超过 1 ~ 2 ng/ml^[20,23-36]。PCT 鉴别病毒性疾病的敏感度和特异性均高于传统标记物(如 C 反应蛋白、白细胞,红细胞沉降率等)^[33,37-38]。近期的一项研究比较了多种生物标记物对于细菌感染和病毒感染的鉴别能力,包括 PCT、IL-1 β 、IL-6、IL-8、IL-10、IL-12、TNF- α 、IFN- γ 、sCD14 等,结果发现 PCT 对于细菌感染的敏感度和特异度最佳,诊断细菌感染的 ROC 曲线下面积达 0.952,此研究中细菌感染的 PCT 中位数为 1.84 ng/ml,而病毒感染的 PCT 中位数为 0.05 ng/ml^[39]。建议对患者检测 PCT 来协助判断病原体是细菌性抑或病毒感染,从而使初始的经验性抗感染治疗具有一定的针对性。

2.3 真菌感染

PCT 的质量浓度依真菌感染的类型而异:侵袭性真菌感染时 PCT 可以增高,局灶性真菌感染 PCT 很少增高,尤其免疫抑制及中性粒细胞减少合并真菌感染时患者的 PCT 不升高。因此 PCT 对真菌感染的诊断价值有限^[40-45]。

已经确诊的真菌感染患者,PCT 的变化趋势可

以作为治疗监测的指标。

长时间抗生素治疗后 PCT 不能恢复到正常范围的感染患者需要考虑合并真菌感染的可能^[46-47]。

3 PCT 水平监测在脓毒症中的应用

3.1 用于脓毒症的诊断和鉴别诊断

脓毒症患者的 PCT 水平明显高于非脓症患者, 细菌性脓毒症患者的 PCT 水平显著高于非细菌性脓毒症。且 PCT 升高对细菌感染导致的脓毒症特异性很高, 因此可作为诊断脓毒症和鉴别严重细菌感染的生物标记物。如果怀疑脓毒症, 建议立刻检查 PCT。目前 PCT 诊断脓毒症的界值水平为 >0.5 ng/ml。PCT <0.05 ng/ml 的患者患高风险细菌性感染的可能性非常小, 也几乎不会发生血流感染^[39,48-53]。

极少数病例因脓毒症起病太快而未达到可检测 PCT 的时间窗 (一般为起病 3~6 h), 因此对于有急性症状而 PCT 水平不高的患者, 建议 6~12 h 后复查 PCT。

3.2 PCT 与血培养阳性率的关系

血培养阳性患者的 PCT 水平较阴性患者高。PCT >0.1 ng/ml 对于入院第 1 天血培养阳性的预测敏感度 100%, 特异性 80%。PCT 在 0.1~0.5 ng/ml 时排除血流感染的阴性预测值在 87%~99%^[10,54-56]。PCT 水平高的患者血培养更易获得病原学结果。有研究证实, 社区获得性肺炎的 (CAP) 患者中, 当 PCT >0.25 ng/ml, 血培养阳性的可能性更大^[57]。

3.3 评估脓毒症严重程度和病情进展情况

PCT 在 SIRS、脓毒症、严重脓毒症和脓毒性休克患者的质量浓度依次增高, 并且具有统计学差异, 与病情的严重程度呈正相关^[49-50,58]。

PCT 质量浓度从 0.5 ng/ml 上升超过 2 ng/ml 时, 严重细菌感染或脓毒症的发生率增高。但是存在严重肝肾功能障碍或手术/外伤后的最初几天, PCT 在 0.5~2 ng/ml 可视为正常范围。PCT 水平超过 2 ng/ml 甚至大于 10 ng/ml 时, 脓毒症、严重脓毒症或脓毒性休克的可能性非常大 (超过 90%)^[49-50]。高水平的 PCT 表明全身炎症反应非常严重, 死亡风险很高, 应立即开始抗生素及其他针对性治疗。

因为 PCT 与脓毒症的病情严重程度相关, 所以动态监测 PCT 水平的变化趋势可以判断病情进展情况。PCT 持续升高提示感染加重或治疗失败,

PCT 降低可以视为感染好转和治疗成功^[59-60]。

建议对下列患者监测 PCT 趋势以评估抗生素治疗以及并发细菌感染的情况:

(1) 监测和评估抗生素治疗效果

①所有接受抗生素治疗的患者; ②需要暂停或者终止抗生素治疗的患者 (建议每天检测); ③需要治疗或监测感染灶的患者 (监控治疗成败和是否合并感染, 例如软组织伤、腹膜炎、肺炎等)。

(2) 监测并发细菌感染的情况

①脓毒症或严重感染风险较高的患者 (例如, 制动、免疫功能缺陷、外伤、手术等) (建议每天检测); ②长期机械通气患者 (具有肺炎和其他院内感染风险); ③置入任何类型的静脉或动脉导管 (有导管相关性感染的风险); ④免疫抑制的患者 (肿瘤、器官移植、化疗、中性粒细胞减少); ⑤手术或创伤后的患者, 如果有任何增加感染风险或怀疑脓毒症的情况; ⑥有二重感染风险的患者 (烧伤、病毒感染); ⑦有非特异性诊断或诊断不明的患者。

3.4 脓毒症预后判断

治疗后 PCT 水平迅速下降通常提示预后良好, 而 PCT 维持原水平或升高则提示预后不良。初始 PCT 水平绝对值的预后意义有限, 即使初始的 PCT 水平非常高, 经过正确的治疗后 PCT 迅速下降, 预后也较好。因而 PCT 的变化趋势对于预后的判断更为重要。

3.5 指导抗生素的使用和监测治疗效果

不同的研究证实, PCT 结合临床信息能够进一步明确抗生素治疗的必要性和优化抗生素疗程。通过每日监测 PCT 作为使用抗生素的指征可使抗生素治疗的疗程缩短, 从而减少了不必要的抗生素使用, 使耐药率和不良反应发生率降低^[61-63]。

①作为开始抗生素治疗的指征:

PCT <0.1 ng/ml 不建议使用抗生素 (取决于临床的实际情况, 甚至可低于 0.25 ng/ml); PCT >0.5 ng/ml 提示存在严重细菌感染或脓毒症, 排除其他导致 PCT 增高的原因, 则需要开始抗生素治疗; 在急诊, PCT >0.25 ng/ml 也可能意味着感染, 如果有其他支持感染的证据则可以开始抗生素治疗。

②作为抗生素疗效判断的标准:

如果 PCT 在治疗开始的 72 h 内每天较前一天下降 30% 以上, 认为治疗有效, 可继续使用原抗生素方案; 如果治疗最初几天内 PCT 水平不降, 提示该治疗

方案效果不佳,应结合临床情况调整治疗方案。

③根据 PCT 水平确定抗生素疗程:

一个抗生素治疗方案持续 1 周左右就应该考虑其有效性,延长疗程应慎重权衡。对某些疾病(如肺炎、尿路感染)或成功去除感染灶后(感染导管拔除)的患者,经 3~5 d 的抗生素治疗后应用 PCT 进行评估。如果 PCT 水平较初始值下降 90% 以上,建议停止抗生素治疗^[61]。

4 影响 PCT 水平的非感染性疾病

除了细菌感染之外,还有很多疾病会导致 PCT 水平增高。见表 2。

4.1 外科手术和创伤

外科手术和创伤后 PCT 可升高,一般在术后第 1、2 天达峰值,峰值可达 2 ng/ml^[64-69]。高水平 PCT 持续时间较短。小型手术和轻微创伤的 PCT 质量浓度一般低于 0.5 ng/ml^[68-74]。术后或创伤后 PCT 增高也可能是并发感染或脓毒症所致,连续检测 PCT 的变化趋势更能与脓毒症进行鉴别。术后 PCT > 5 ng/ml 是出现并发症的预测因素^[75-77]。

4.2 器官移植

器官移植后的急性排异反应与感染的临床表现类似,研究发现急性排异反应时 CRP 和白细胞计数增高,而 PCT 水平正常。使用免疫抑制剂不会明显抑制 PCT 的产生^[75-85]。

①肝移植:

肝移植后几乎总是有 PCT 增高,由于术后合并感染和脓毒症会导致病死率显著增高,所以建议术后第 1 天就开始监测 PCT 水平。

②心脏移植和心肺联合移植:

心脏移植和心肺联合移植术后第 1 天或第 2 天 PCT 升高到 2 ng/ml 然后迅速降低属于术后反应。但是在任何情况下超过 10 ng/ml 均应认为是合并严重感染或脓毒症^[81-82]。在移植前检查供体的 PCT 水平可为移植成功提供依据。供体的 PCT 水平较高会导致受体更容易发生并发症。诊断界值为 2 ng/ml (敏感度 36%, 特异性 89%)^[86]。

③肾移植:

肾移植诱导 PCT 较少^[85,87-88],术后感染和脓毒症的发生率也不高,因此不推荐常规监测 PCT。仅在怀疑感染或脓毒症时检测。需要结合肾移植前的基础 PCT 水平判断术后 PCT 的临床意义^[89-91]。

4.3 肾功能不全

肾脏对 PCT 的清除不是影响 PCT 血浆质量浓

度的决定因素^[92],但是严重肾功能不全(肌酐清除率 < 25 ml/min)的患者,建议使用 0.5~1.5 ng/ml 作为脓毒症的诊断界值。PCT 增高的肾功能不全患者应首先考虑合并脓毒症。

4.4 肿瘤

肿瘤性疾病一般不会诱导 PCT 生成,肿瘤性疾病 PCT 平均水平 < 0.5 ng/ml。但是甲状腺髓样细胞癌或甲状腺滤泡癌除外,在此种情况下 PCT 可作为肿瘤标记物之一^[93-97]。

肿瘤广泛转移的患者 PCT 水平轻度增高。肝转移的 PCT 水平在 0.5 ng/ml 左右,而全身转移时 PCT 可高达 1 ng/ml^[98]。

4.5 血液系统疾病

血液系统疾病或肿瘤一般不会引起 PCT 增高。但是有些例外的情况,比如急性淋巴细胞性白血病、急性髓样细胞样白血病、B 细胞淋巴瘤、何杰金淋巴瘤以及正在进行化疗的儿童患者。在这些情况下,建议使用更高的界值(0.5~1 ng/ml)诊断脓毒症^[99-103]。

中性粒细胞减少症合并感染时 PCT 的诱导受到抑制而仅轻度增高,完全性中性粒细胞减少症的患者 PCT 生成减少,仅为正常的 1/2~1/3^[104-105]。因此建议使用较低的界值来评估此类患者是否合并细菌感染(0.1~0.25 ng/ml)^[106-109]。此类患者合并严重脓毒症和脓毒性休克时,PCT 的诊断灵敏度和特异性仍然很高^[106,110-112]。

骨髓移植和造血干细胞移植后 PCT 也有轻度增高,但是很少超过 0.1~1 ng/ml。合并严重感染时 PCT 水平显著增高。但是在此类患者监测 PCT 的变化趋势是否可以用于确定抗生素治疗的必要性或有效性尚待进一步研究证实。

4.6 自身免疫性疾病

自身免疫性疾病一般不会导致 PCT 增高,但也有例外的情况,例如抗中性粒细胞抗体阳性血管炎、肺出血-肾炎综合征、川崎病、少年型类风湿性关节炎、自身免疫性肝炎、原发性硬化性胆管炎。这些疾病 PCT 质量浓度可超过 0.5 ng/ml,有时达到 3 ng/ml^[30,113-119]。目前的资料显示,95% 的自身免疫病 PCT < 0.5 ng/ml,中位数是 0.2 ng/ml。有小样本的研究推荐使用 PCT > 1 ng/ml 作为自身免疫性疾病合并感染的诊断界值,目前尚未见大样本的研究结果^[113]。

4.7 胰腺炎

急性胰腺炎是引起 SIRS 的重要非感染性疾病。

胰腺炎患者 PCT 质量浓度的分布范围很宽, 与是否合并细菌感染没有必然的联系。高水平 PCT 是病情严重、出现器官功能障碍和预后不良的指征。如果胰腺炎患者的 PCT > 1 ng/ml, 则感染性坏死的可能性增加且预后不良。因此对胰腺炎患者不能仅凭 PCT 的水平做出治疗决策, 需要结合其他的评价手段^[120-121]。

5 结论

急诊科需要检测 PCT 的疾病有很多。感染性疾病的诊断、分层、治疗和预后评估, 以及合理使用抗生素、防止耐药率增高、控制耐药菌过快增长、合理使用医疗资源, PCT 都是一个有力的辅助工具。以往 PCT 监测在 ICU 使用比较普遍, 急诊科是 ICU 病患的主要来源, 应该提高急诊科医师对于 PCT 监测的重视程度, 从可疑感染性疾病的患者一开始进入医院, 就做好诊断和治疗监控, 为后续的治疗打好基础。

(陈云霞执笔)

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(收稿日期: 2012-07-03)

(本文编辑: 郑辛甜)

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刊名: [中华急诊医学杂志](#) 

英文刊名: [Chinese Journal of Emergency Medicine](#)

年, 卷(期): 2012, 21(9)

本文链接: http://d.g.wanfangdata.com.cn/Periodical_jzyx201209005.aspx