血降钙素原水平（PCT）支持下的临床诊疗与抗菌药物管理

医院感染管理科

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主　题

PCT的背景介绍

PCT连续监测的意义

PCT用于指导抗生素管理

PCT局限性

PCT对细菌感染反应具有专一性

机体在受到细菌感染后，随着细胞因子如IL-6，IL-1 β，TNF-α的释放，PCT被诱导产生，释放到血流，使血液中PCT浓度上升。

正常情况下，PCT只是降钙素合成过程中的中间产物,在细菌感染时,可由多种细胞和器官产生的

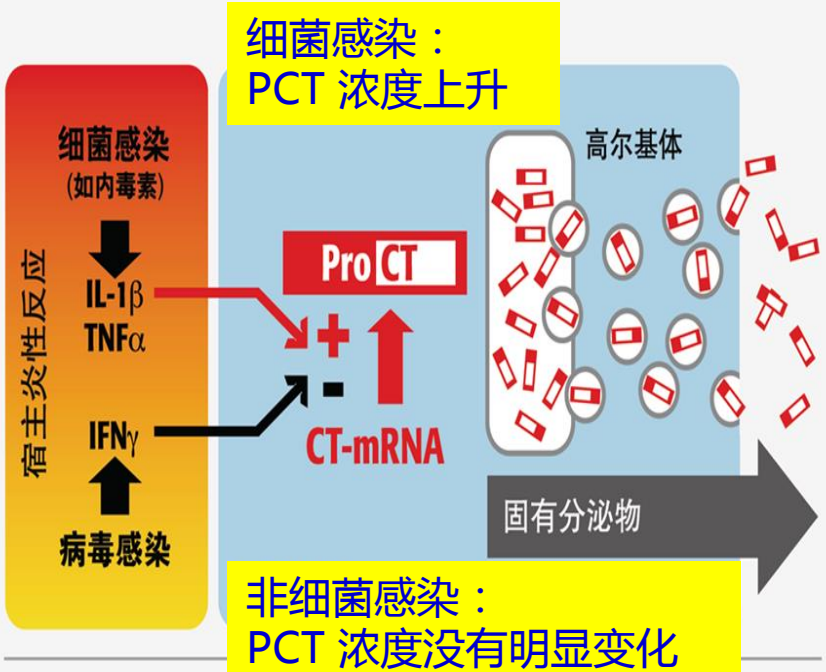
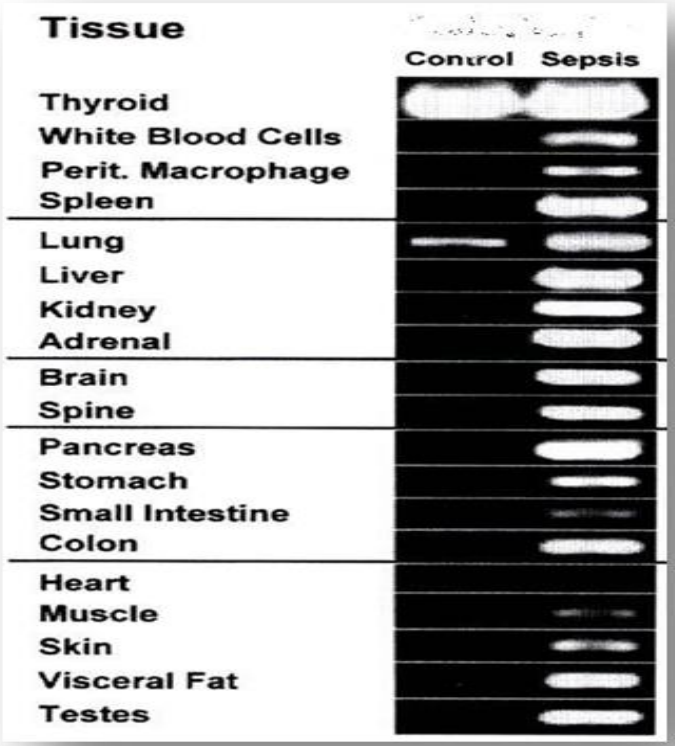


图2: CALC-I基因表达调控的原理图，在患脓毒症期间该基因的表达导致了PCT在细胞中的释放。

改编自 Christ-Crain M 等 Swiss Medical Weekly 2005;135(31-32):451-460. [7]

Pro-CT: 降钙素的激素原. CT-mRNA: 降钙素信使核糖核酸



9. Müller B. et al., JCEM 2001

PCT对于疾病监测有着天然的优势

PCT

4h左右开始释放；

6h-12h左右快速上升；

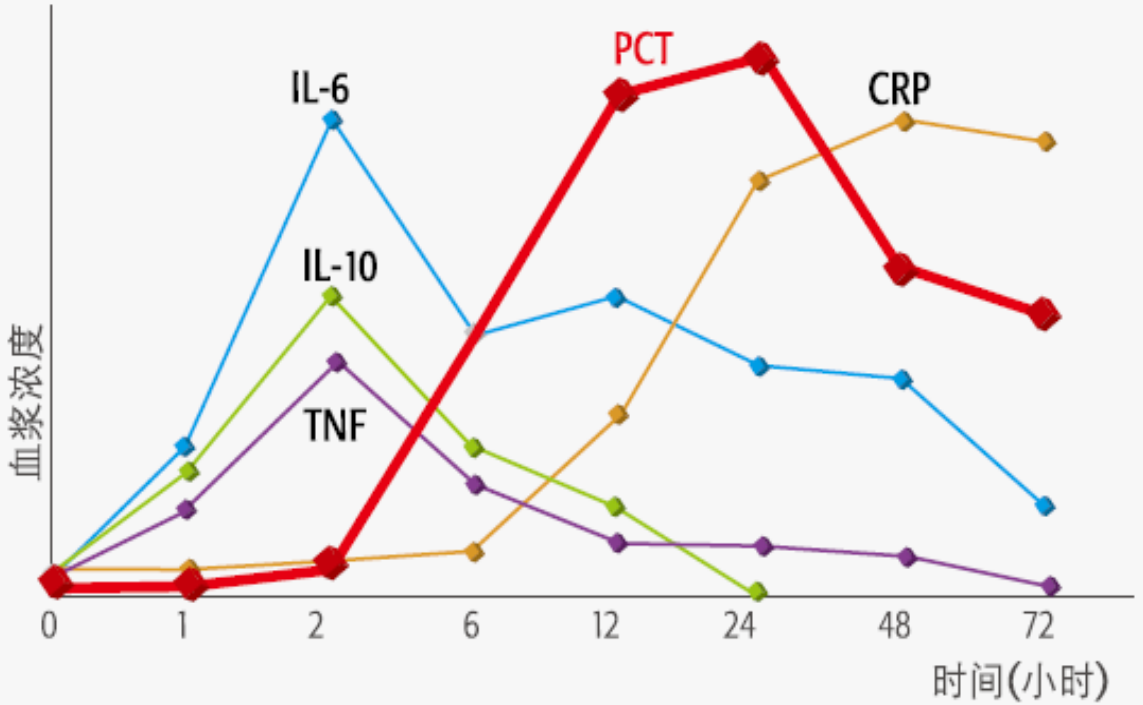
半衰期约24h，感染控制可快速衰减；

CRP

12-24h左右开始释放

20-72h左右快速上升

平台期长，3-7D



志愿者体内**注入 E.coli toxin，间隔时间抽血观察PCT、CRP、IL-6、IL-10、TNF**的动力学改变。

Reinhart K, et al. Crit Care Clin 2006;22;503-519

对脓毒症的诊断、预后及治疗监测各生物学指标的评估性能

An Informal Categorization of Biomarkers of Sepsis

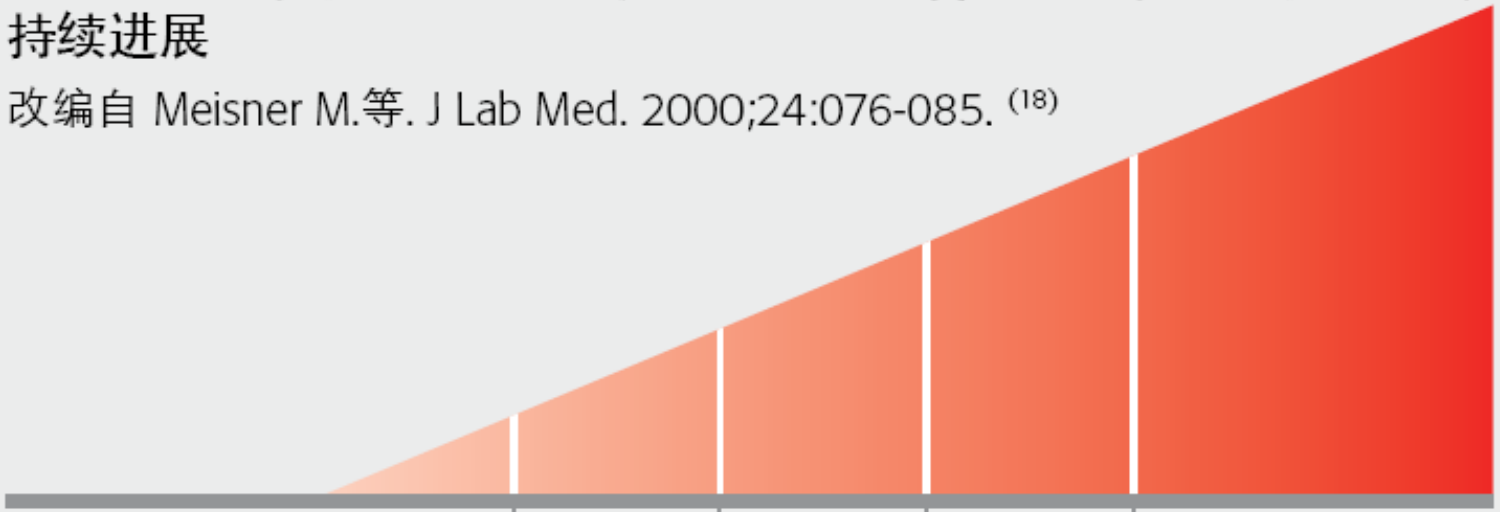
	诊断	预后	监测
Marker	**Diagnosis**	**Prognosis**	**Monitoring**
Procalcitonin	+++	+++	+++
Interleukin 6	++	+++	++
White cell count	++	+	++
Endotoxin	++	++	++
C-reactive protein	++	++	++
HLA-DR	+	+++	++
Protein C	+	++	+
IL-10	+	++	+
HMG-1	++	++	++

Report of the 5th Toronto Sepsis Roundtable, Toronto, Ontario, Canada, October 25, 26, 2000.

PCT在脓毒症早期诊断中的价值

图4: PCT水平增加反映了从健康状况到重度脓毒症和脓毒性休克的持续进展

改编自 Meisner M.等. J Lab Med. 2000;24:076-085. [18]



- ✓ 为了达到最佳诊断效果，应根据病人的急性程度(风险水平)和临床情况来调整PCT的临界值。

Prognostic value of procalcitonin in infection-related mortality of cancer patients

Ali Murat Sedef[1], Fatih Kose[1], Ahmet Taner Sumbul[1], Ozlem Dogan[2], Ebru Kursun[3], Zafer Yurdakul[4], Bilge Sumbul Gultepe[5], Huseyin Mertsoylu[1], Ahmet Sezer[1], Ozgur Ozyilkan[1]

[1]Department of Medical Oncology, [2]Department of Internal Medicine, [3]Department of Infectious Diseases, [4]Department of Biochemistry, Baskent University, Adana; [5]Department of Microbiology, Bezmi Alem Vakif University, Adana, Turkey

- ✓ Statistical analysis showed a significant relationship between PCT levels and mortality (p=0.001)
- ✓ The mortality rate of patients with a PCT value > 2 ng/mL was 34.3%, compared with 9.6% in patients with a PCT below this value (p=0.005).
- ✓ Furthermore, PCT predicted in-ward cancer patient mortality with a sensitivity of 66% and a specificity of 76%.

- ✓ PCT水平与癌症病人死亡率有良好的相关性
- ✓ PCT水平高于> 2 ng/mL 时，死亡率达到34.3%，；低于该水平时，死亡率为9.6%
- ✓ PCT预测内脏相关的癌症，灵敏度为66%，特异性为76%.

JBUON 2016; 21(3): 740-744

PCT与肿瘤病人死亡率的相关性优于传统标志物

PCT-病死率 ROC曲线

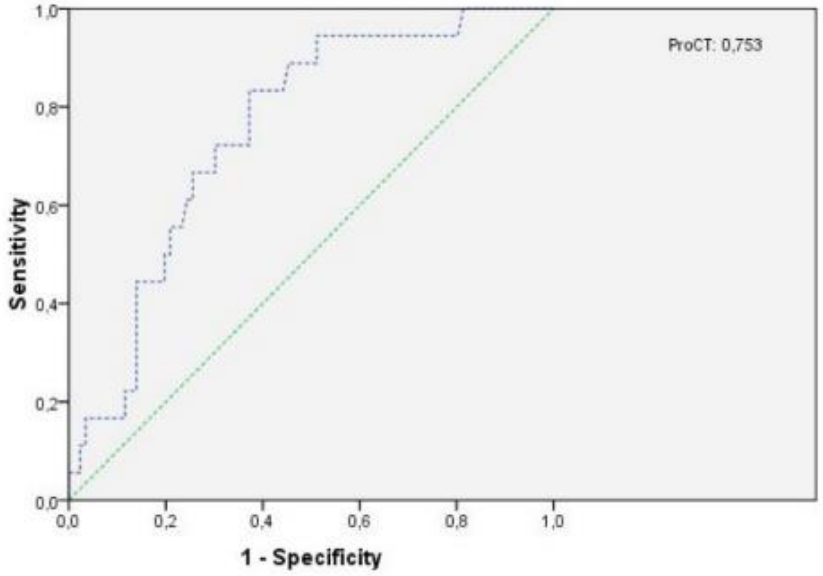


Figure 1. Receiver operating characteristic (ROC) curve for procalcitonin (ProCT) for infection-related mortality. The area under the curve for ProCT is 0.753 with p <0.0001.

CRP/ESR-病死率 ROC曲线

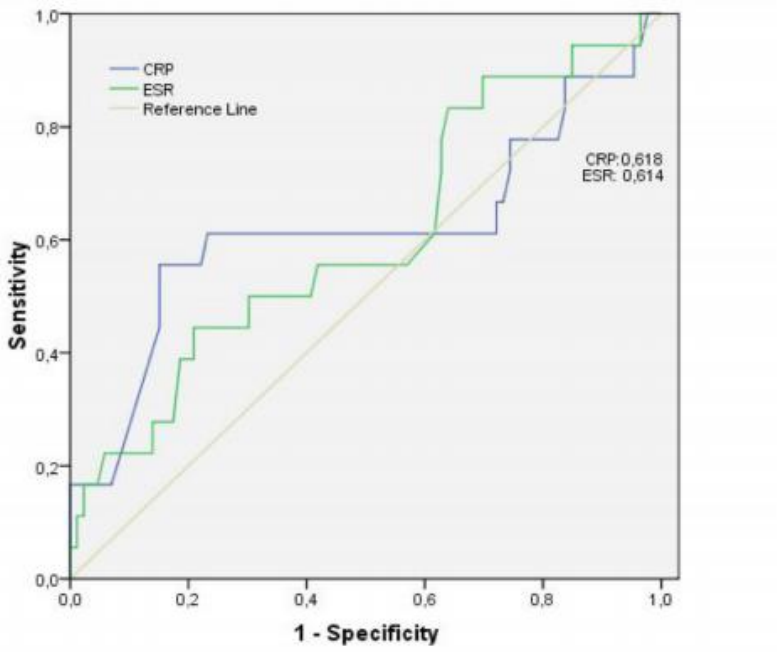


Figure 2. Receiver operating characteristic (ROC) curve for CRP and ESR for infection-related mortality. The area under the curve for CRP and ESR was 0.618 and 0.614, respectively, with p>0.05.

Original Article

Can Procalcitonin Distinguish Infectious Fever From Tumor-Related Fever in Non-Neutropenic Cancer Patients?

William Shomali, MD[1]; Ray Hachem, MD[1]; Anne-Marie Chaftari, MD[1]; Ying Jiang, MS[1]; Ramez Bahu, MD[1]; Joseph Jabbour, BS[1]; Sammy Raad, BS[1]; Munirah Al Shuaibi, MD[1]; Iba Al Wohoush, MD[1]; and Issam Raad, MD[1]

研究对象：248位 罹患实体瘤/淋巴瘤/多发性骨髓瘤的非粒细胞减少发热患者

血流感染
局部感染
无感染证明
肿瘤相关发热

Table 2. Comparison of Baseline Procalcitonin (PCT) Levels Between Patients With and Without Infections

Group	N	Median PCT (Range)	*P*
Bloodstream infection	30	1.06 (0.075-81.95)	
Localized bacterial infection	60	0.30 (0.075-154.7)	.048
No documented infection	141	0.31 (0.075-68.6)	.011
Tumor-related fever	8	0.67 (0.11-4.14)	.71

P values are the result of comparing PCT levels between patients with bloodstream infection and other groups.

William Shomali, et,al. Cancer 2012;118:5823-29.

PCT：细菌感染/脓毒症疗效与预后监测

通过PCT不断在体内衰减，反映出抗生素治疗策略的成功

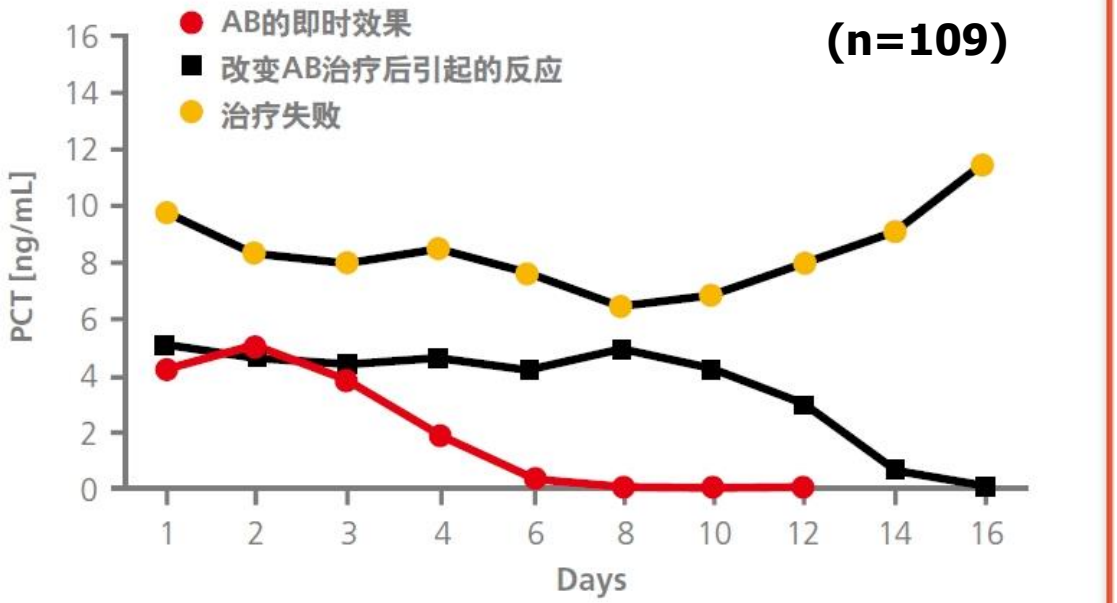
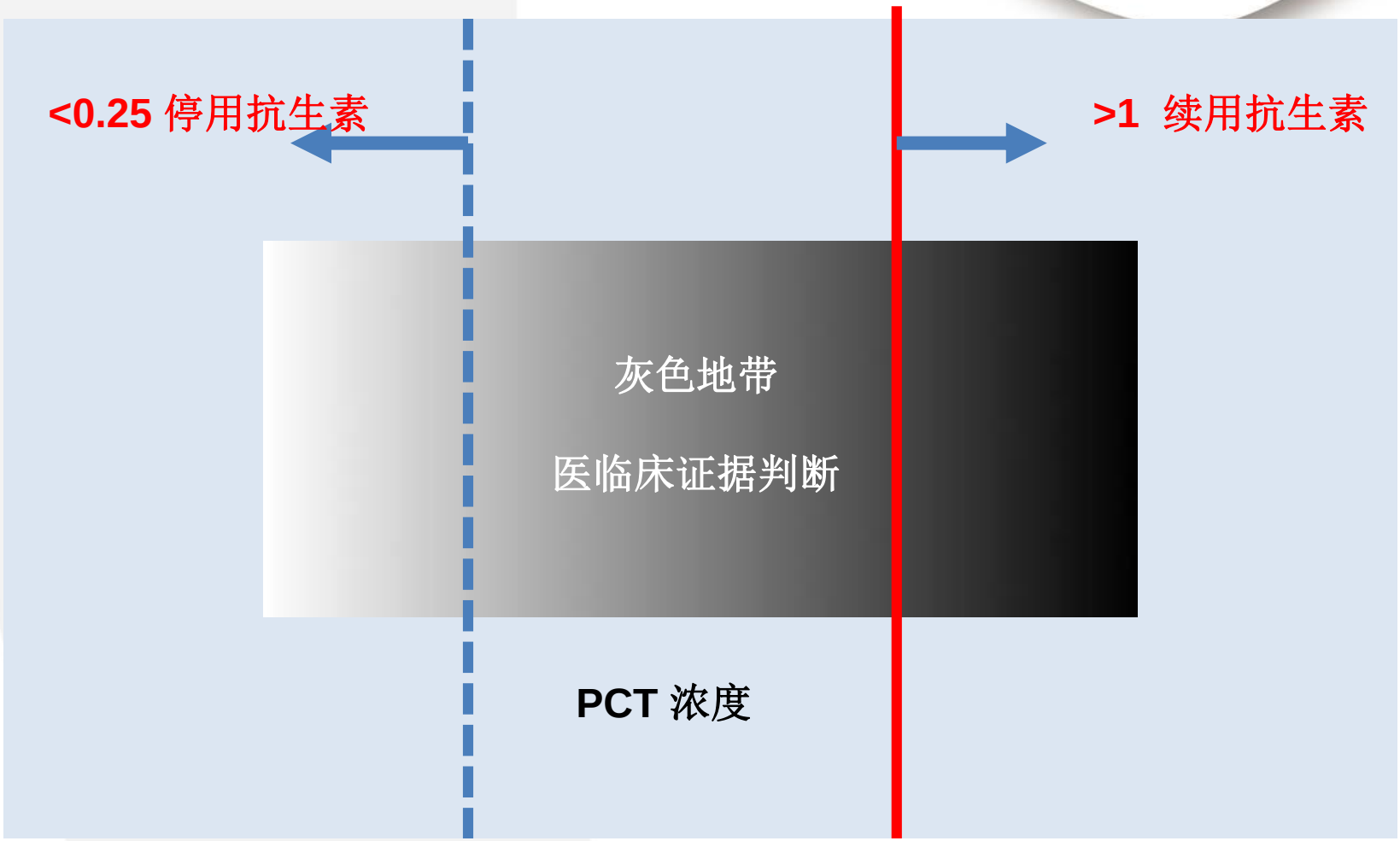


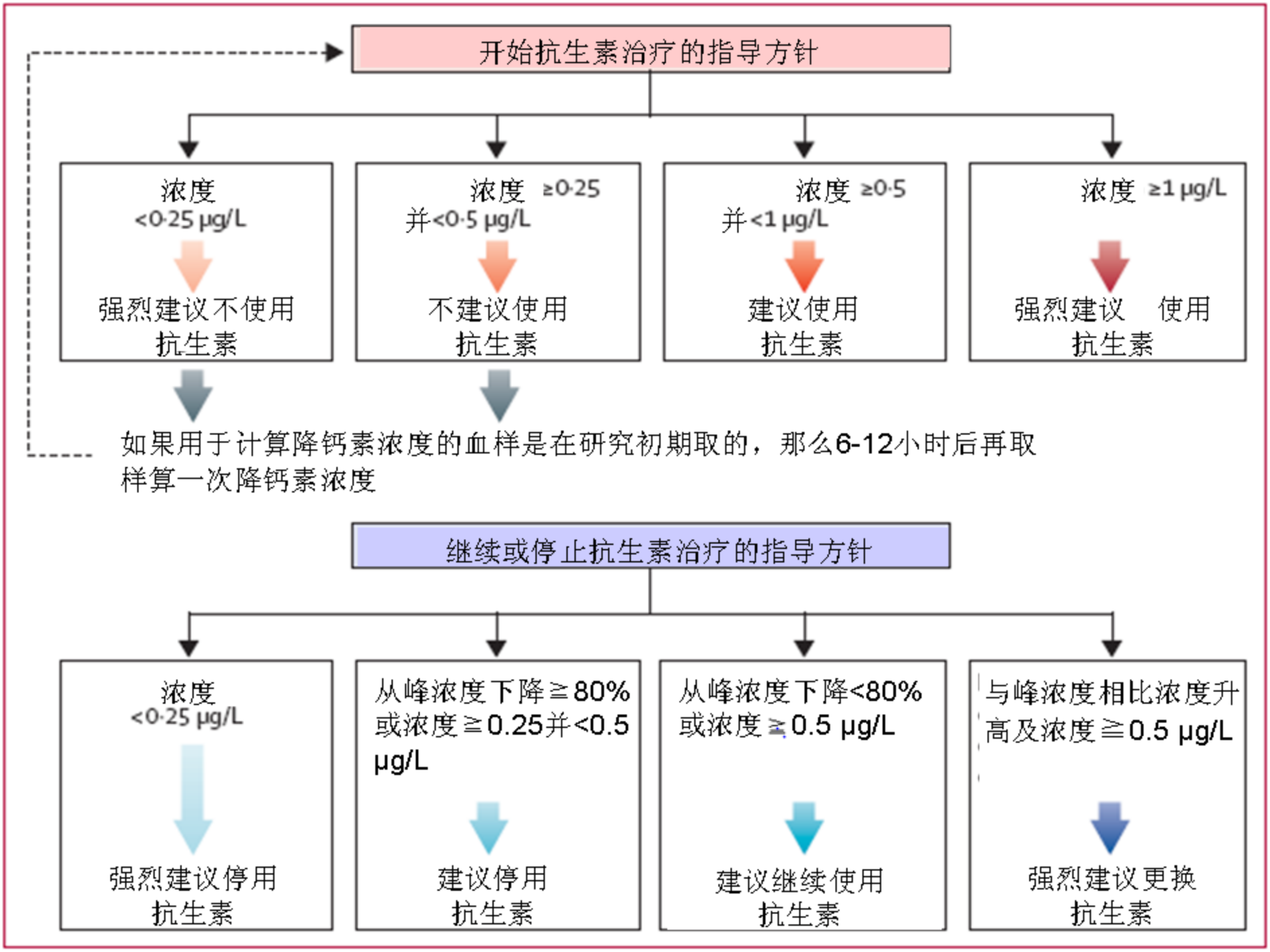
图6 随患者对抗生素治疗的响应，引起了PCT血清水平的典型变化过程（n=109）。[11]

随着患者对抗生素治疗的响应，引起了PCT血中浓度水平的典型变化过程

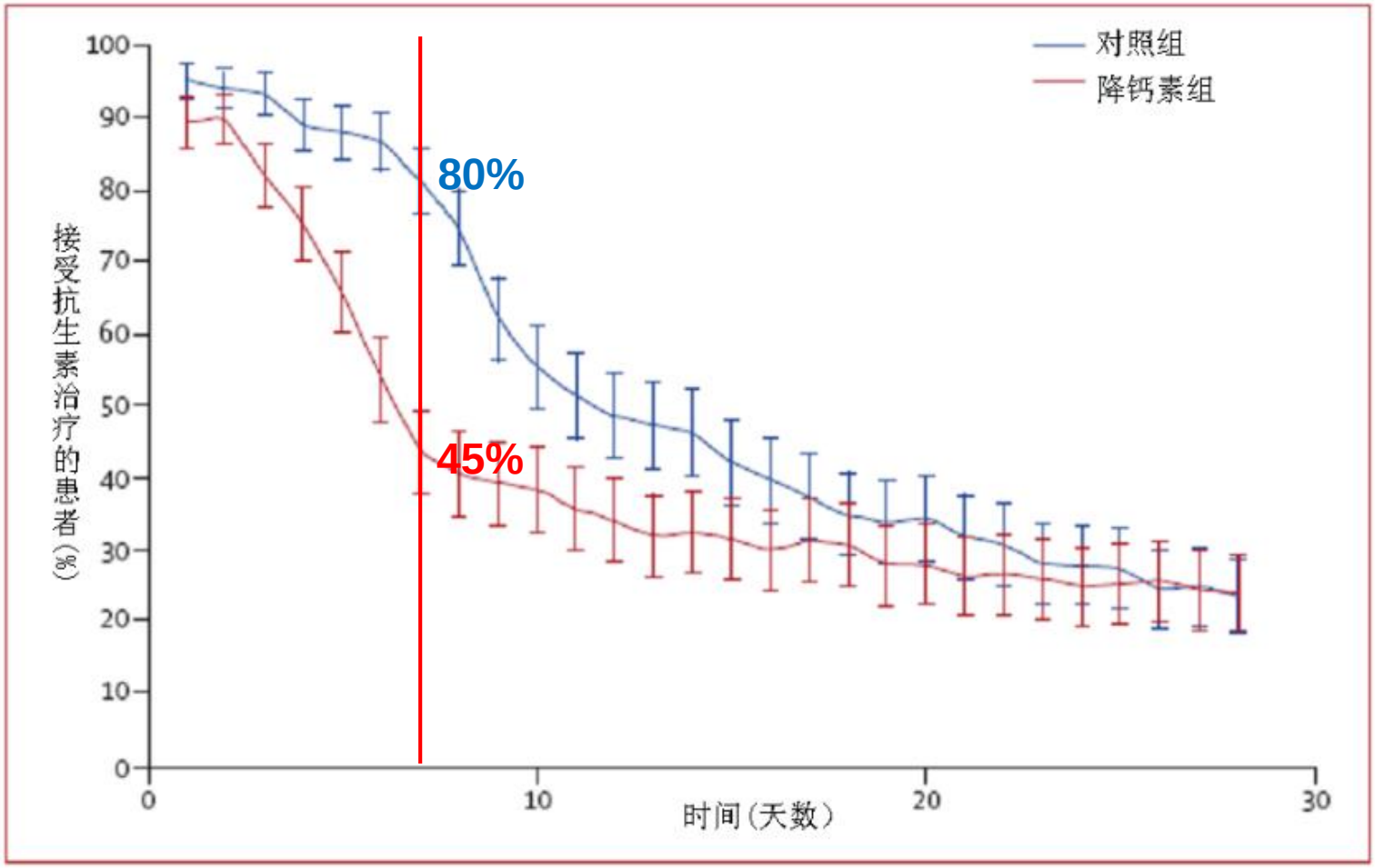
F. Stüber, University Bonn, Lecture at ISICEM, Brussels 2001

灰色地带



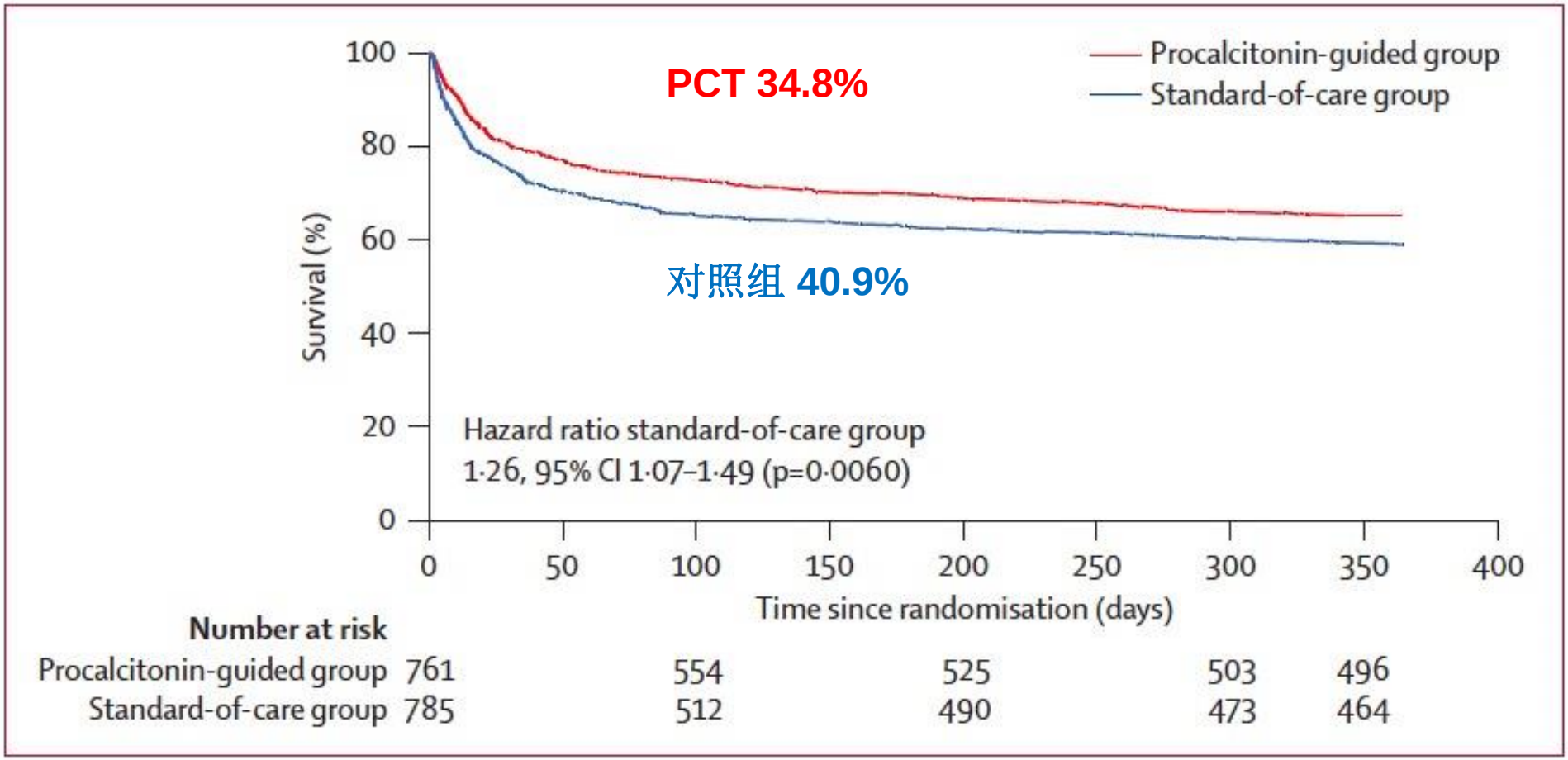

开始抗生素治疗的指导方针
浓度 <0·25 μg/L
强烈建议不使用抗生素
浓度 ≥0·25 并<0·5 μg/L
不建议使用抗生素
浓度 ≥0·5 并<1 μg/L
建议使用抗生素
浓度 ≥1 μg/L
强烈建议 使用抗生素
如果用于计算降钙素浓度的血样是在研究初期取的，那么6-12小时后再取样算一次降钙素浓度
继续或停止抗生素治疗的指导方针
浓度 <0·25 μg/L
强烈建议停用抗生素
从峰浓度下降≥80%或浓度≥0.25并<0.5 μg/L
建议停用抗生素
从峰浓度下降<80%或浓度≥0.5 μg/L
建议继续使用抗生素
与峰浓度相比浓度升高及浓度≥0.5 μg/L
强烈建议更换抗生素

第1-28天接受抗生素治疗的患者对比



对于降钙素原组的患者，在研究开始的第28天后，组内患者不使用抗生素的平均天数与对照组相比增加2.7天，抗生素使用降幅达23%。

PCT指导停药组死亡率明显低于对照组



Lancet Infect Dis 2016；16:819-27

PCT指导停药组
有效减少抗生素使用，降低病人负担

	Procalcitonin-guided group (n=761)	Standard-of-care group (n=785)	Between-group absolute difference in means (95% CI)	p value
Antibiotic consumption (days) 抗生素使用天数				
Daily defined doses in first 28 days	7·5 (4·0 to 12·8)	9·3 (5·0 to 16·5)	2·69 (1·26 to 4·12)	<0·0001
Duration of treatment	5·0 (3·0 to 9·0)	7·0 (4·0 to 11·0)	1·22 (0·65 to 1·78)	<0·0001
Antibiotic-free days in first 28 days	7·0 (0·0 to 14·5)	5·0 (0 to 13·0)	1·31 (0·52 to 2·09)	0·0016
Mortality (%)				
28-day mortality 28天死亡率	149 (19·6%)	196 (25·0%)	5·4% (1·2 to 9·5)	0·0122
1-year mortality 1年死亡率	265 (34·8%)	321 (40·9%)	6·1% (1·2 to 10·9)	0·0158
Adverse events				
Reinfection	38 (5·0)	23 (2·9)	−2·1% (−4·1 to −0·1)	0·0492
Repeated course of antibiotics	175 (23·0)	173 (22·0)	−1·0% (−5·1 to 3·2)	0·67
Time (days) between stop and reinstitution of antibiotics	4·0 (2·0 to 8·0)	4·0 (2·0 to 8·0)	−0·22 (−1·31 to 0·88)	0·96
Costs 抗生素治疗费用				
Total cumulative costs of antibiotics	€150 082	€181 263	NA	NA
Median cumulative costs antibiotics per patient	€107 (51 to 229)	€129 (66 to 273)	€33·6 (2·5 to 64·8)	0·0006
Length of stay (days) 住院天数				
On the intensive care unit	8·5 (5·0 to 17·0)	9·0 (4·0 to 17·0)	−0·21 (−0·92 to 1·60)	0·56
In hospital	22·0 (13·0 to 39·3)	22·0 (12·0 to 40·0)	0·39 (−2·69 to 3·46)	0·77

Data are median (IQR), n (%), or mean (95% CI). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs. NA=not applicable.

Table 2: **Primary and secondary outcome measures**

PCT检测：局限性

- ✓ 非特异性PCT诱因-可能的假阳性结果包括
  - ✓ 手术创伤、多处创伤：在手术后的前两天
  - ✓ 出生48小时以内的新生儿
  - ✓ 免疫刺激药物 (OKT3,TNFa,IL-2.)
  - ✓ 严重烧伤
  - ✓ 肾功能不全
  - ✓ 中暑
- ✓ PCT略微增加
  - ✓ 感染早期 (→ 6-12 小時后重新检测!)
  - ✓ 之前进行过有效的抗生素治疗
  - ✓ 非典型性肺炎(肺炎支原体、肺炎衣原体)
  - ✓ 局部感染 (肾炎)

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REVIEW

Utility of blood procalcitonin concentration in the management of cancer patients with infections

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OncoTargets and Therapy
22 January 2016
Number of times this article has been viewed

Conclusion and perspective for the future

In summary, evaluation of blood PCT might be very helpful in the management of cancer patients who frequently suffer from infections, but clinicians should be aware of some interpretative problems and limitations. In general, the highest plasma levels of PCT are observed in severe, acute bacterial infections, mainly BSI, but it could be also elevated in infection-independent conditions (multiple trauma, major surgery, cardiogenic shock) and in the presence of metastasis or carcinoma with a neuroendocrine component. In patients

在以下特定情况下，PCT会升高：

多处创伤

大型手术

心源性休克

肿瘤转移性疾病

神经内分泌癌

慢性肾功能不全

肿瘤转移病人PCT基础值更高

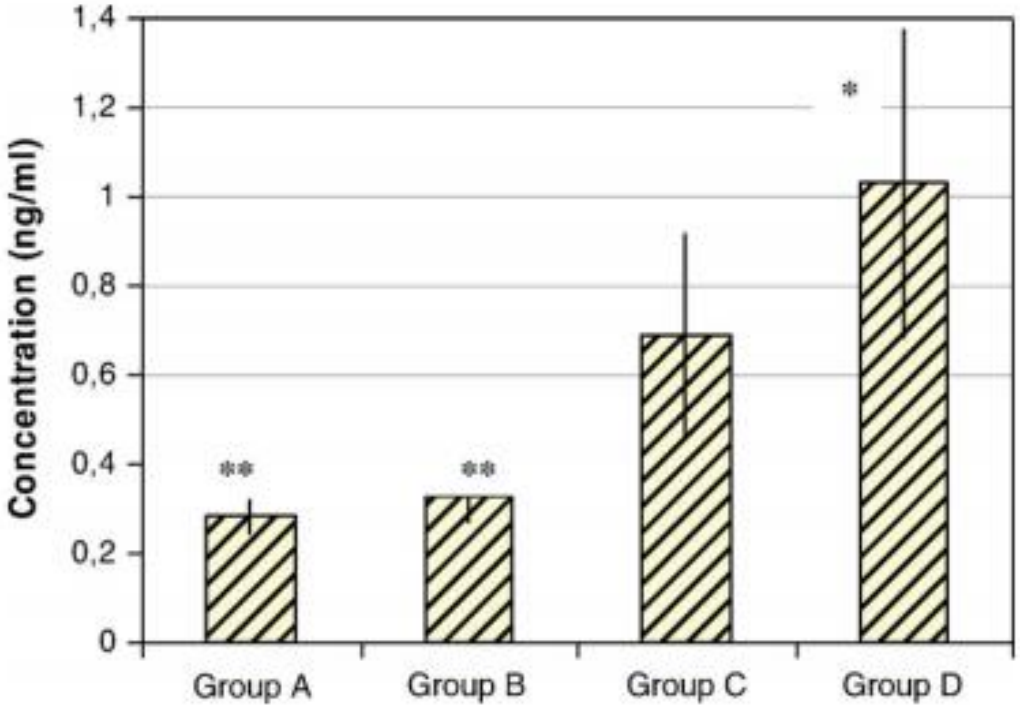


Fig. 1. Serum procalcitonin (PCT, ng/mL) levels in the studied groups. Patients with generalized carcinoma (group D) present significantly higher levels of serum PCT when compared with controls (group A) and/or patients without metastasis (group B). Data are presented as means±S.E.; *$p<0.05$ vs. group C; **vs. group D. Statistical significant difference is referred after correction by Bonferroni.

(group A), 15 名-健康人群对照组

(group B), 21名-实体瘤+非转移病人

(group C) 11名 肝转移病人

(group D) 11名 广泛转移病人

Clinical Biochemistry 40 (2007) 336–342

异常值的临床解读

1. 新生儿生理性升高？

   出生48小时内有为生理性升高，48小时后可参考成人参考节点（0.5），建议持续送检确认是否感染

2. G+细菌和G-细菌的PCT是否有显著差异？

   文献报道G-细菌感染患者PCT更高，原因为G-细菌分泌大量LPS刺激PCT分泌

3. 真菌感染PCT是否升高？

   非侵蚀性真菌感染会轻微升高，但连续监测时如果持续维持0.1-2,高度怀疑真菌感染

4. PCT已经降下来了，CRP依然在高值，如何解释？

   PCT半衰期更短，是连续监测的最佳指标

5. 手术后PCT很高，是否提示感染？

   术后48h内PCT会出现生理性升高，已有研究提示，连续监测PCT可预测是否存在感染

同时送检无菌体液培养，有助于明确感染病原体

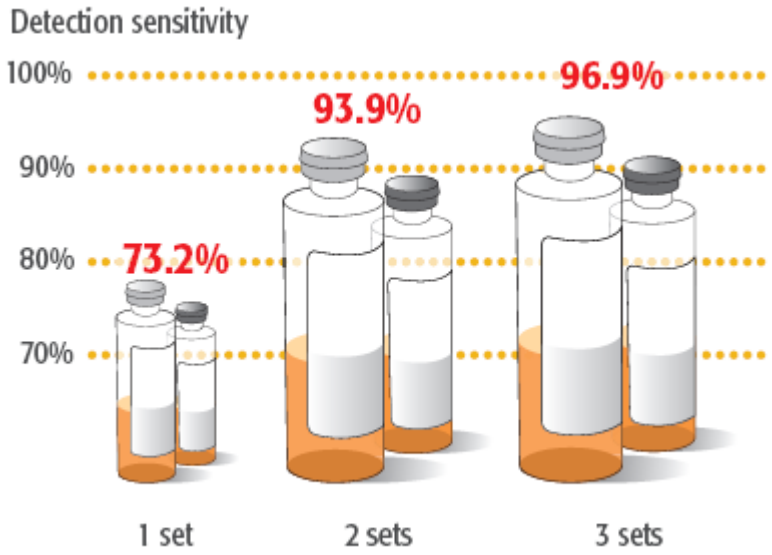
增加血培养采集套数能够提升阳性率

The number of blood culture sets improves the yield of pathogen recovery

With two blood culture sets, the % of pathogen recovery is above 90%

增加血培养的采集套数，可以有效地增加病源菌的复苏比例

当采用双套血培养时，病源菌的复苏比例可以达到90%



双瓶双侧送检：

1. **提升阳性率**
2. **有助于排除污染**

Cumulative sensitivity of blood culture sets[16]

Weinstein et al. Detection of Bloodstream Infections in Adults: How Many Blood Cultures Are Needed J Clin Microbiol. 2007; 45:3546-3548

低值PCT意义

——PCT与真菌感染

深部真菌感染PCT值	
培养结果	PCT值
白假丝酵母菌	0.58
白假丝酵母菌	0.2
白假丝酵母菌	1.32
无名假丝酵母	0.13
新型隐球菌	0.23
新型隐球菌	0.06
新型隐球菌	0.18

逆向思维：对免疫功能低下的患者，如果PCT长期在灰色浓度间起伏、血培养阴性、但又存在炎性症状，可考虑真菌感染可能？？

小结

- ✓ PCT动态监测
  - ✓ 可以用于下呼吸道感染（LRTI）和脓毒症诊疗
  - ✓ 辅助指导抗生素合理使用，帮助临床医生做出重要决策
  - ✓ 可降低患者住院时间和医疗支出
- ✓ PCT联合规范病原学检测
  - ✓ 一快一慢，提升诊断阳性率
  - ✓ 协助污染排查，尽早明确病原菌，开启靶向治疗