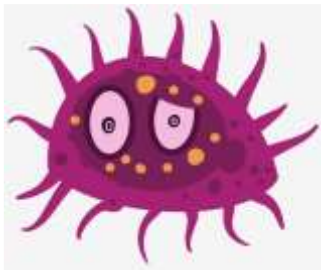
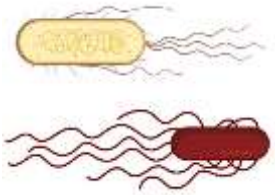
Practical Use of **Biomarkers** in Infection Management: **Experience Sharing** on **Antibiotic** Stewardship and Therapy Optimization

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Intensivist & I.D. 簡修洵 醫師/教授

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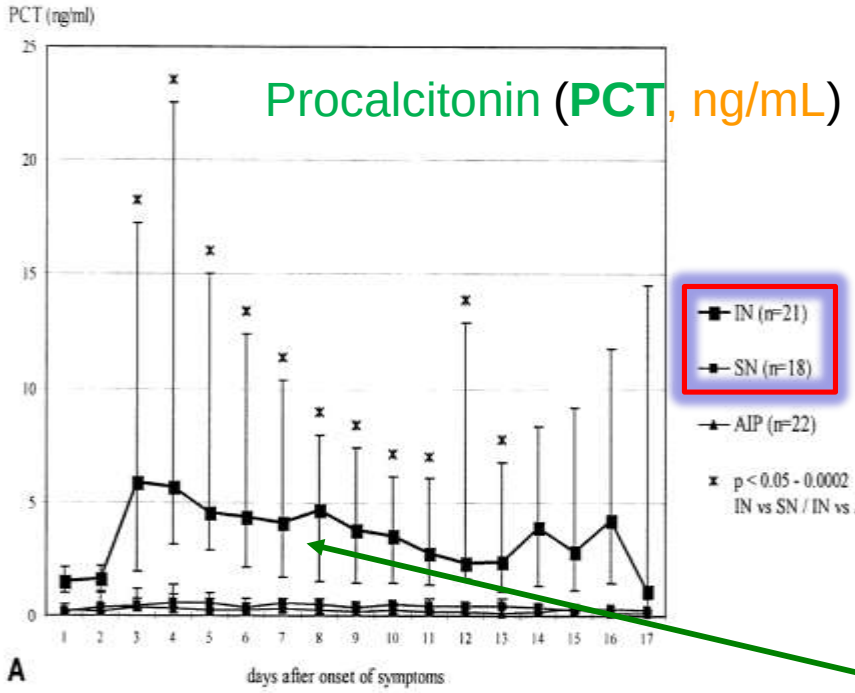
- What non-infectious factors likely **increase** plasma procalcitonin (**PCT**) concentration ?
- Application in lower respiratory tract infection management (algorithm) ?
- In different stages in hepatic and renal function injury -----> Differences in **baseline** plasma **PCT** concentration among pts without infection ?
- Significant **determinants** for plasma **PCT** concentrations, regarding monomicrobial GNB bacteremia among adult pts ?
- Invasive candidiasis, & primary **VRE** BSI → plasma median **PCT** concentrations, **diagnostic value** ?

Procalcitonin (PCT)

- In 1981, **PCT** (116 amino-acid glycoprotein, 1.3 kDa) was discovered in human thyroid medullary carcinoma, and was synthesized (when inflammation occurs) in almost all parenchymal tissues.
- The diagnostic value of **PCT** is significantly better than presepsin, IL-6, & IL-8 among patients admitted with suspected sepsis.
- The **PCT non-clearance** is strongly associated with all-cause mortality in septic patients (the **48-h** PCT clearance **>30**% --> survival [HR **2.90**; 95% CI 1.22 to 6.90]).
- **PCT** concentration, medians & ranges: substantial differences in **GNB** vs. **GPC**, **fungi**, and **viral** infections.

The Clinical Value of **Procalcitonin**, in the Prediction of Infected Necrosis (IN), in **Acute Pancreatitis**

Intensive Care Med 2000;**26**:S159-64 Rau B et al



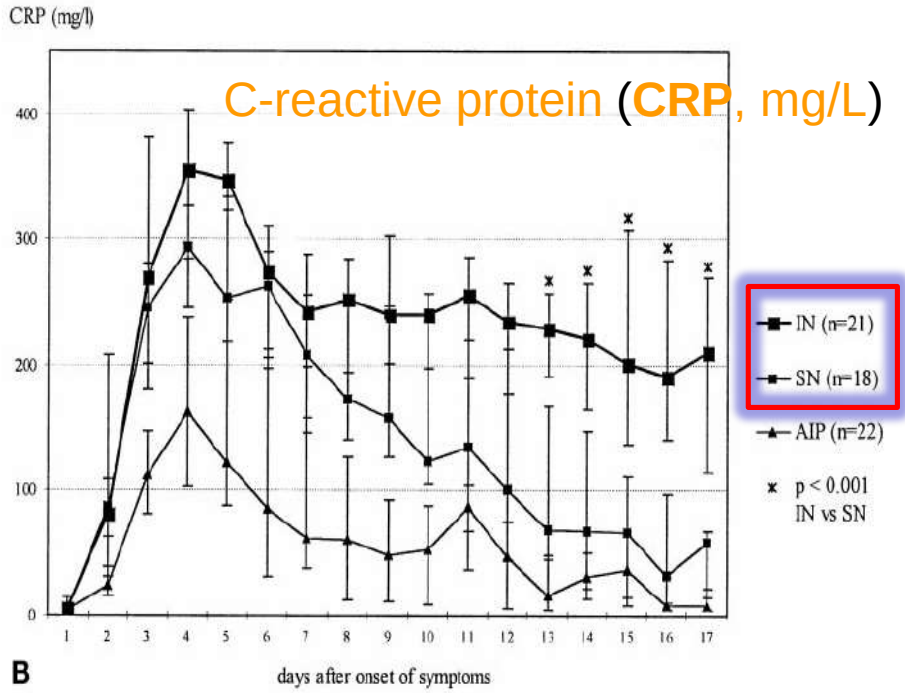


Figure. Course of **PCT** (**A**) and **CRP** (**B**) in patients with **infected necrosis** (**IN**), **sterile necrosis** (**SN**), and **interstitial edematous pancreatitis** (**AIP**). **PCT** concentrations were significantly higher from day 3-13 after onset of symptoms in patients with **IN**, whereas CRP revealed ***no*** difference between **IN** and **SN** during day 1-7.

Factors other than infections predispose into elevation of plasma [procalcitonin] ? (1)

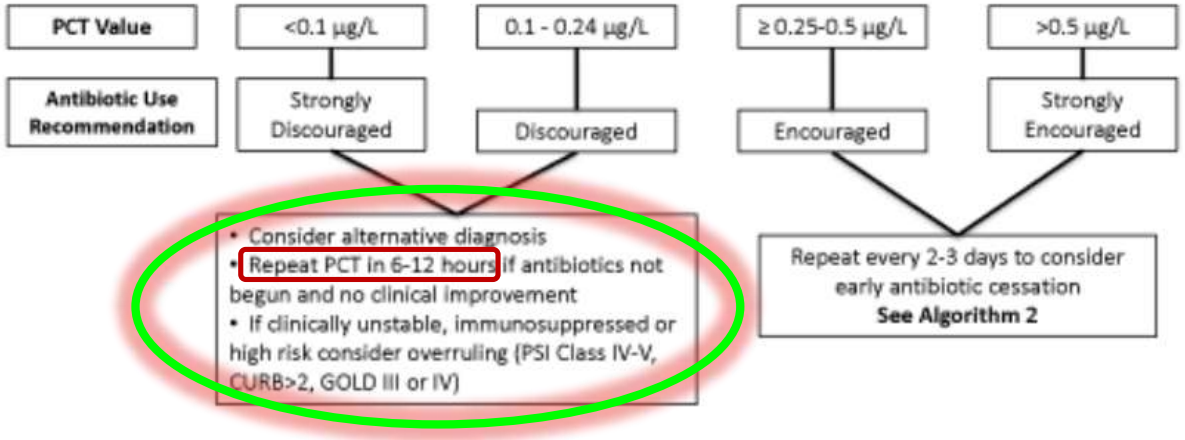
- **Shock** & **Ischemia**: Prolonged cardiogenic shock, severe hypoperfusion, & ischemic bowel syndrome (sterile inflammatory activation).
- Specific **Malignancies**: Certain tumors—particularly (**1**) medullary thyroid carcinoma, and (**2**) small cell lung cancer (SCLC)—actively synthesize and release PCT.
- Major **Tissue Trauma** & **Burns**: Severe physical injury, extensive surgery, and thermal burns.

Factors other than infections predispose into elevation of plasma [procalcitonin] ? (2)

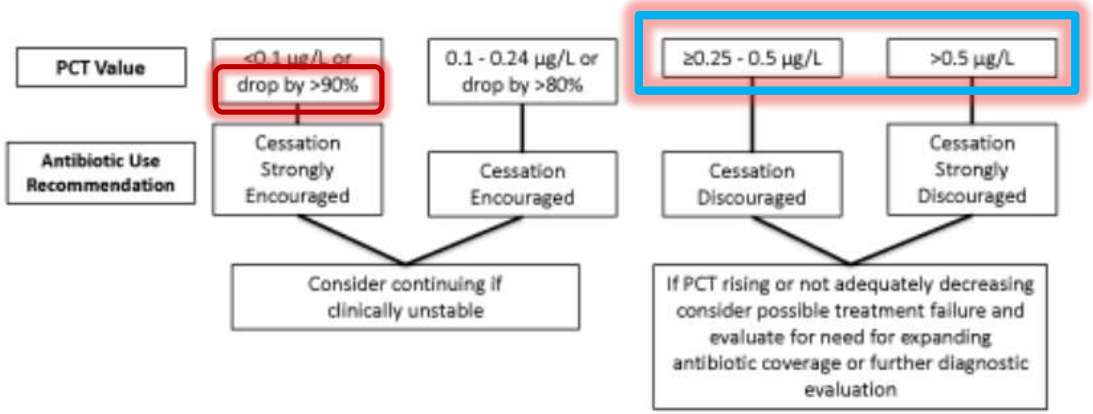
- Severe **Systemic Inflammation**: Non-infectious systemic conditions, e.g., severe acute pancreatitis, heat stroke, or diabetic ketoacidosis (DKA).
- **Renal Failure**: Acute kidney injury, or acute liver disease—reduced renal clearance of this peptide.
- **Medications** & Therapies: (**1**) Immunomodulatory drugs (e.g., anti-thymocyte globulin, alemtuzumab), and (**2**) granulocyte colony-stimulating factors (**G-CSF**)—stimulate cytokine release, thus elevate PCT.

PCT Interpretations in: lower respiratory tract infections (pneumonia, COPD exacerbation, bronchitis)

(1) LRTI Initial Antibiotic Use Algorithm



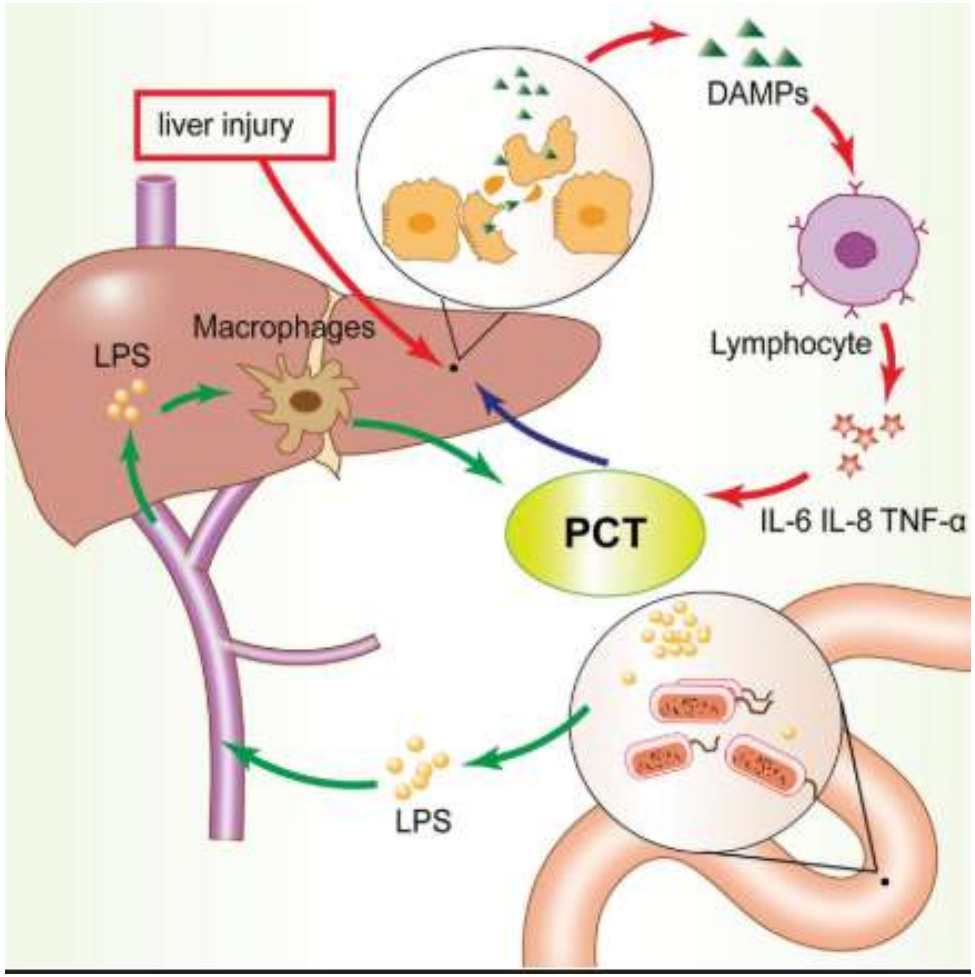
(2) LRTI PCT Follow up Algorithm



Algorithm 2: LRTI PCT Value Follow Up

Procalcitonin and Liver Disease: A Literature Review

J Clin Transl Hepatol 2019 Mar 28;**7**(1):51-5 Dong R et al



1. Rule et al. found that PCT values in chronic liver disease (**0.104** ng/mL) --- significantly differed from acute liver failure (ALF; **2.0** ng/mL --- above a cut-off that generally indicates severe sepsis. *PLoS One* 2015;**10**:e0138566
2. Damage-associated molecular patterns (**DAMPs**): Liver (and other organ) injury results in the death of a vast amount of liver cells; through sensors and effector cells, DAMPs are released.
3. **Endotoxins** on GNB: once recognized by the host toll-like **receptor 4** on immune cells, inflammation-related cytokines (TNF-α, IL-1/6/8/10) are immediately produced as well; thus inducing the PCT synthesis process.

∴在急性肝功能損傷(ALF)的病人,利用plasma [**PCT**] 來診斷是否有 sepsis 的 threshold上,應該要往上調整

Kidney Impairment vs. plasma [PCT] ?

1. Acute kidney injury (AKI):

- Frequently accompanied by profound systemic inflammatory responses (e.g., severe infections, major surgery, or shock).
- AKI patients typically exhibit significantly higher and more erratic PCT elevations compared to CKD patients with the same GFR.

2. Chronic kidney disease (CKD):

- Usually involving a slow, progressive decline in kidney function and is associated with chronic, low-grade systemic inflammation and oxidative stress.
- Stable CKD generally exhibit a mild, and predictable elevation in baseline PCT that correlates with the severity and stage of their disease. However, the magnitude of this baseline PCT elevation (in non-infected CKD patients) is usually lower than that seen in severe AKI.

AKI, stable CKD, & ESRD patients, differences in plasma [PCT] diagnostic thresholds ?

J Pharm Technol 2020 Aug;**36**(4):157-63 Bowman C et al

Table 3. PCT Thresholds in Renal Dysfunction From Prior Literature.

	Number of patients	Definition of renal dysfunction	Threshold	Sensitivity	Specificity	AUC
Park et al[16]	493	eGFR <60 mL/min/1.73 m^2	1.1 ng/mL	73%	89%	0.867
Lu et al[1]	803	N/A	0.5 ng/mL	68%	94%	0.82
El-Sayed et al[18]	473	eGFR ≤30 mL/min/1.73 m^2	3.2 ng/mL	53%	75%	0.67
Lee et al[17]	41	ESRD on dialysis (either hemodialysis or peritoneal dialysis)	0.75 ng/mL	76.2%	80%	N/A
Nakamura et al[19]	806	KDIGO AKI guidelines	Stage 1: 0.74 ng/mL	83.8%	91.6%	0.910
			Stage 2: 0.59 ng/mL	75%	88.9%	0.867
			Stage 3: 4.07 ng/mL	87.2%	93.5%	0.946
Bowman et al (current study)	198	Overall: CrCl ≤60 mL/min calculated by Cockcroft-Gault	Overall: 1.0 ng/mL	59%	76%	0.736
		AKI: KDIGO AKI guidelines	AKI: 1.5 ng/mL	59%	86%	0.797
		CKD: GFR <60 mL/min/1.73 m^2 at baseline, corroborated with provider documentation in the patient's history and physical	CKD: 0.1 ng/mL	66%	64%	0.683
		ESRD: GFR <15 mL/min/1.73 m^2	ESRD: 1.5 ng/mL	80%	65%	0.714

Abbreviations: PCT, procalcitonin; AUC, area under the curve; eGFR, estimated glomerular filtration rate; N/A, not applicable; ESRD, end-stage renal disease; KDIGO, Kidney Disease Improving Global Outcomes; AKI, acute kidney injury; CrCl, creatinine clearance; CKD, chronic kidney disease.

Plasma [PCT] among non-infectious AKI pts: correlate with serum [creatinine]

個人淺見 for diagnostic [PCT] thresholds --- (1) AKI, **0.75-1.50** ng/mL; (2) CKD, **0.25** ng/mL; (3) ESRD (most delay in PCT clearance, & susceptible to inflammation), **1.00-1.75** ng/mL

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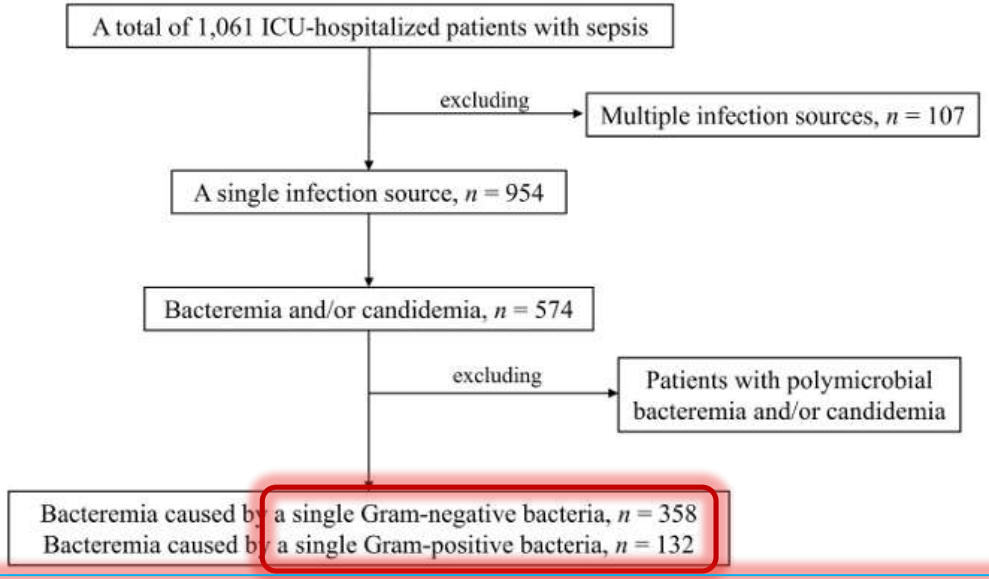
journal homepage: www.e-jmii.com

Significant determinants of plasma procalcitonin concentrations in adult patients hospitalized in intensive care units with monomicrobial Gram-negative bacteremia (1)

J Microbiol Immunol Infect 2026 Jun;**59**(3):403-10 **Jean SS** et al

Chih-Cheng Lai [a,b,g], Chun-Chung Hsueh [c,g], Ching-Ting Wei [d,g], I-Min Liu [e], Po-Chuen Hsieh [e], Shio-Shin Jean [e,f,*]



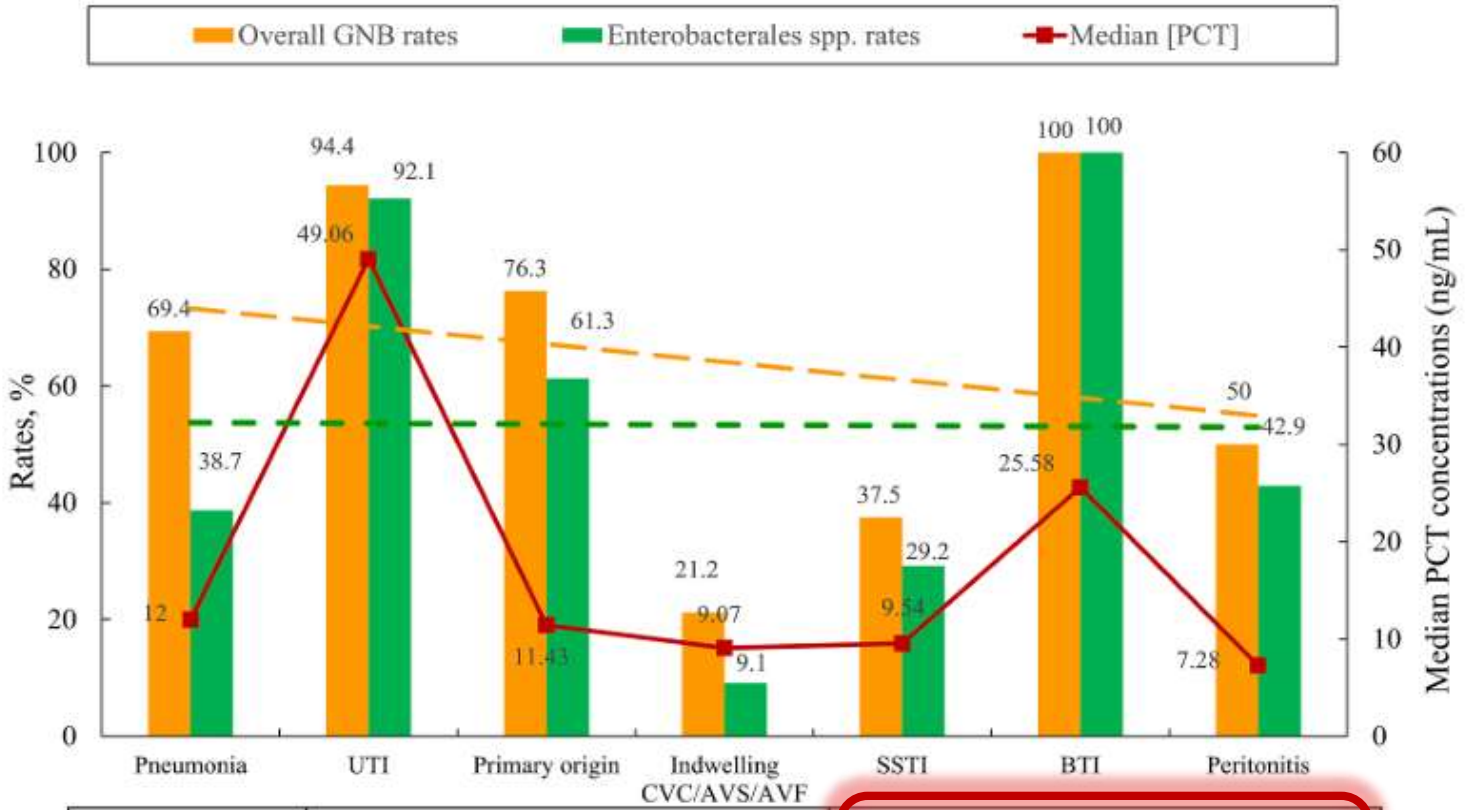
Median (IQR) [**CRP**] & [**PCT**], **GNB%** among various infection sources

Main sources of bacteremia caused by a single bacterium (number)	GNB rates, isolate no. [%] (Enterobacterales/ non-fermenting GNB)	CRP, median (IQR), mg/dL	PCT, median (IQR), ng/mL
Pneumonia (*n* = 127)	86[a] [67.7 %] (48 [37.8 %]/36 [28.3 %])	17.37 (8.09, 26.94)	12.68 (2.63, 33.27)
Urinary tract infection (*n* = 122)	118 [96.7 %] (114 [93.4 %]/4 [3.4 %])	15.50 (8.14, 25.16)	46.59 (11.43, 104.86)
Primary bacteremia (*n* = 93)	71 [76.3 %] (57 [61.3 %]/14 [15.1 %])	14.20 (4.76, 20.67)	6.90 (2.53, 41.09)
Indwelling central venous catheter, or arteriovenous shunt infections (*n* = 33)	7 [21.2 %] (3 [9.1 %]/4 [12.1 %])	15.91 (5.30, 20.01)	12.09 (5.61,59.01)
Skin and soft tissue infections (*n* = 24)	9 [37.5 %] (7 [29.2 %]/2 [8.3 %])	19.02 (9.21, 31.89)	17.61 (2.57, 52.27)
Biliary tract infections (*n* = 24)	24 [100 %] (24 [100 %]/0 [0 %])	13.75 (8.08, 22.32)	28.75 (5.07, 64.95)
Peritonitis, primary or secondary (*n* = 14)	7 [50 %] (6 [42.9 %]/1 [7.1 %])	15.04 (10.58, 26.65)	17.87 (7.01, 27.23)

∴ [**CRP**] 比 [**PCT**] 在 ICU 的感染, 更難區分感染源的種類

Significant determinants of plasma [PCT] for monomicrobial GNB bacteremia in ICU adult patients (2)

J Microbiol Immunol Infect 2026 Jun;**59**(3):403-10 **Jean SS** et al



Coefficients	Median [PCT] vs. Overall GNB rates	Median [PCT] vs. Enterobacterales rates
r	0.703	0.767
P values	0.078	0.044

Fig. 2. Correlation between the proportions of Enterobacterales isolates and overall Gram-negative bacteria (GNB; with associated dotted trendlines), and median plasma procalcitonin concentrations across seven predominant bloodstream infection sources in patients with monomicrobial bacteremia hospitalized in intensive care units between 2020 and 2024 spp., species. [PCT], procalcitonin concentration. UTI, urinary tract infection. CVC, central venous catheter. AVS, arteriovenous shunt. AVF, arteriovenous fistula. SSTI, skin and soft tissue infection. BTI, biliary tract infection.

Significant determinants of plasma [PCT] for monomicrobial GNB bacteremia in ICU adult patients (3)

J Microbiol Immunol Infect 2026 Jun;**59**(3):403-10 **Jean SS** et al

利用 Comparable time-to-positive (T2P) durations 的 subgroups, 來做分析:

- (**1**) **Shock** development, and (**2**) a APACHE II score **>21** points: predict Pittsburgh bacteremia score (**PBS**) ≥4 (OR, 4.92 and 9.33, both *P* values <0.001).
- In contrast, Enterobacterales as the etiological organism: negatively associated with a PBS ≥4 (OR, 0.31; *P* = 0.011).
- Etiological **GNB** isolates, 表現出 MDR phenotype (including ESBL-producing *E. coli*, CR-*A. baumannii*, & CR-*K. pneumoniae*): no impact on [**PCT**].
- **DIC**: presents higher plasma [**PCT**] than no DIC (*P* = 0.031).
- Immunodeficient group (including Pugh-Child **C** liver cirrhosis): presents relatively lower plasma [**PCT**] (*P* = **0.062**), whereas no difference after Child C liver cirrhosis was excluded (*P* = 0.946).

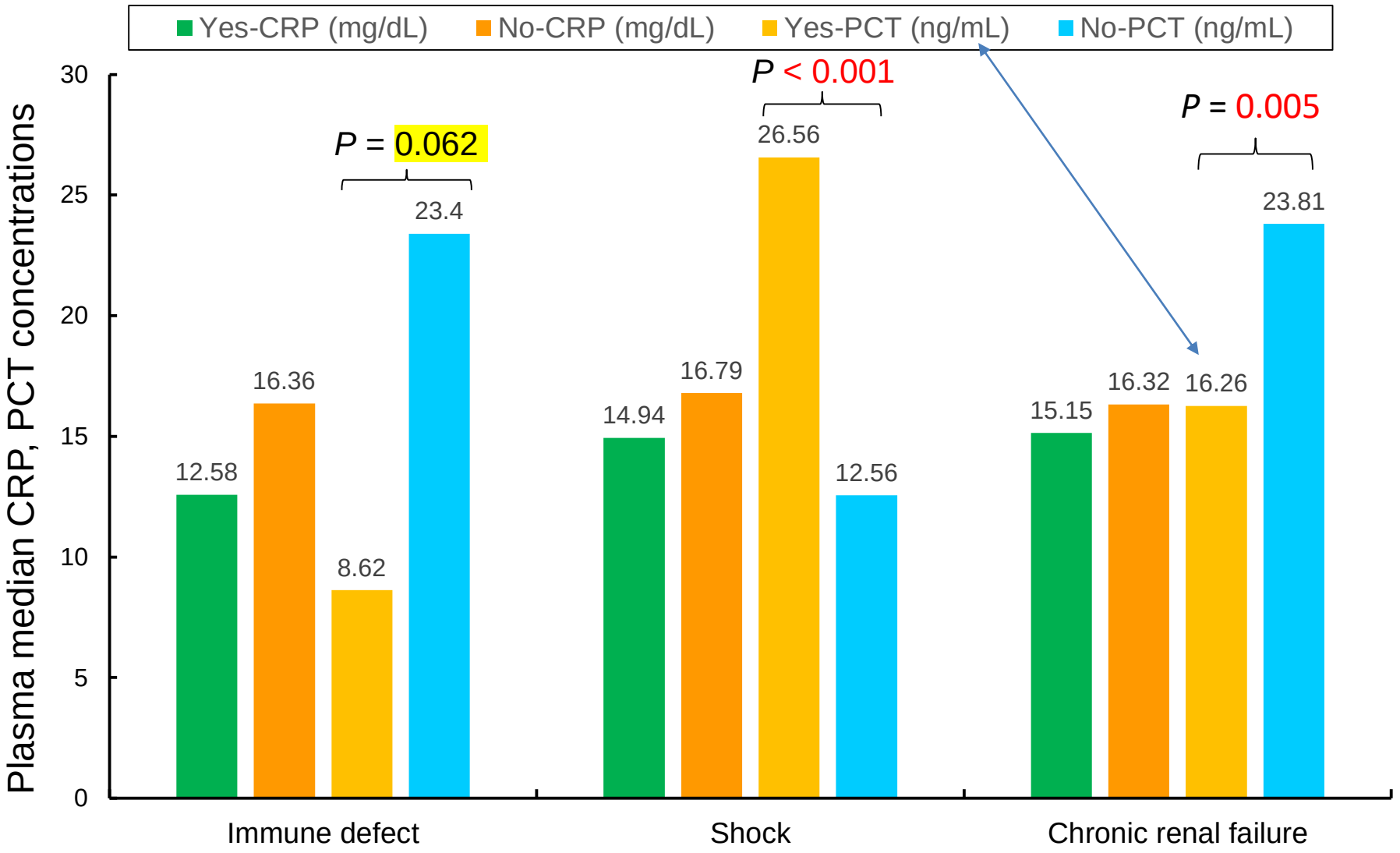
Pitt bacteremia score (PBS) assessing **severity of septicemia** (1998 version)

Int J Antimicrob Agents 1999, Chow JW, Yu VL

Fever (oral)	Point(s)
≤ 35.0° C	**2**
36.0 ° C	**1**
36.1~ 38.9 ° C	**0**
39.0 ° C	**1**
≥ 40.0 ° C	**2**
Hypotension	**2**
(A) Acute hypotensive event drip in systolic > 30 mmHg and diastolic > 20 mmHg	
(B) Requirement for intravenous presor agents; or	
(C) Systolic blood pressure < 90 mmHg	
Mechanical ventilation	**2**
Cardiac arrest	**4**
Mental status : Alert	**0**
Disoriented	**1**
Stuporous	**2**
Comatous	**4**

Critically ill condition : ≥ 4 points !

Gram (-) bacteria 革蘭氏陰性菌 (*n*=362)



T2P, median (IQR), hours	Yes	[n=59] 36 (14, 57)	[n=258] 35.5 (15, 54.25)	[n=78] 37.5 (17, 57.5)
	No	[n=299] 40 (16, 54)	[n=100] 41 (17, 54)	[n=280] 38.5 (15, 53.75)

Calcitonin Precursors (**Procalcitonin**) are Reliable Markers of Sepsis in a Medical ICU

Crit Care Med 2000;**28**:977-83 Müller B et al

Table. Evaluation of laboratory parameters, for the diagnosis of ***sepsis*** in a medical intensive care units (**%**)

Parameter	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value
Calcitonin precursor (1 ng/mL)	**89**	**94**	**90**	**94**
Interleukin-6 (50 pg/mL)	65	79	71	74
C-reactive protein (**10 mg/dL**)	**71**	**78**	**74**	**75**
Lactate (2 mmol/L)	40	77	58	61

High serum concentrations of **procalcitonin**: associated with ***poor*** **prognosis** (***P*** = **0.01**). However, are they ***true*** in real-world scenarios ???

Significant determinants of plasma [PCT] for monomicrobial GNB bacteremia in ICU adult patients (4)

J Microbiol Immunol Infect 2026 Jun;**59**(3):403-10 **Jean SS** et al

∴ **High** plasma [PCT] in GNB septicemia 不一定會造成病人有高的死亡率; 另外 (independent predictors 中): (**1**) shock, (**2**) UTI with hydronephrosis, 或 (**3**) DM 的病人, plasma [PCT] 會有比較高的傾向; 反之, **Child C** liver cirrhosis 的病人, plasma [PCT] 有明顯降低的傾向

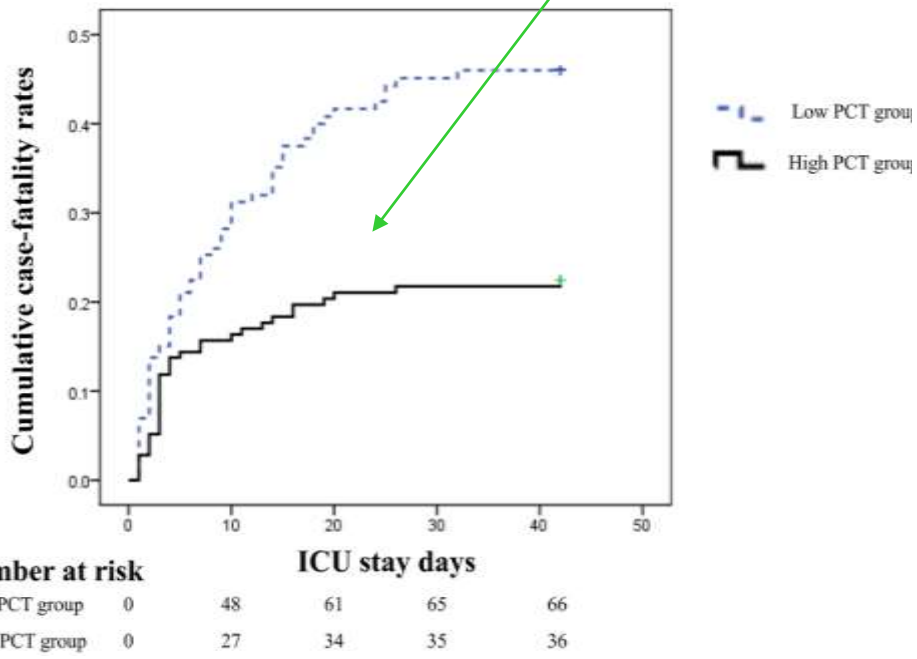


Table 4

Independent factors predicting significant impacts on plasma procalcitonin concentrations among sepsis patients with monomicrobial Gram-negative bacteremia.

Analyzed characteristics	odds ratio	95 % confidence interval	*P* values
Charlson Comorbidity Index ≥3 points	0.633	0.373–1.073	0.090
Immunodeficient conditions	1.432	0.645–3.179	0.378
Shock development	2.094	1.253–3.500	0.005
Enterobacterales species causing infections	1.049	0.536–2.053	0.888
Multidrug-resistant phenotypes	0.816	0.475–1.402	0.462
Urinary tract infection	1.048	0.515–2.136	0.896
Urinary tract infection with hydronephrosis	3.826	1.640–8.926	0.002
Pneumonia	0.670	0.335–1.342	0.259
Primary source	0.665	0.338–1.309	0.238
Diabetes mellitus	1.656	1.016–2.699	0.043
Child–Pugh class C liver cirrhosis	0.352	0.113–0.967	0.049
Chronic obstructive pulmonary disease	0.676	0.205–2.229	0.520

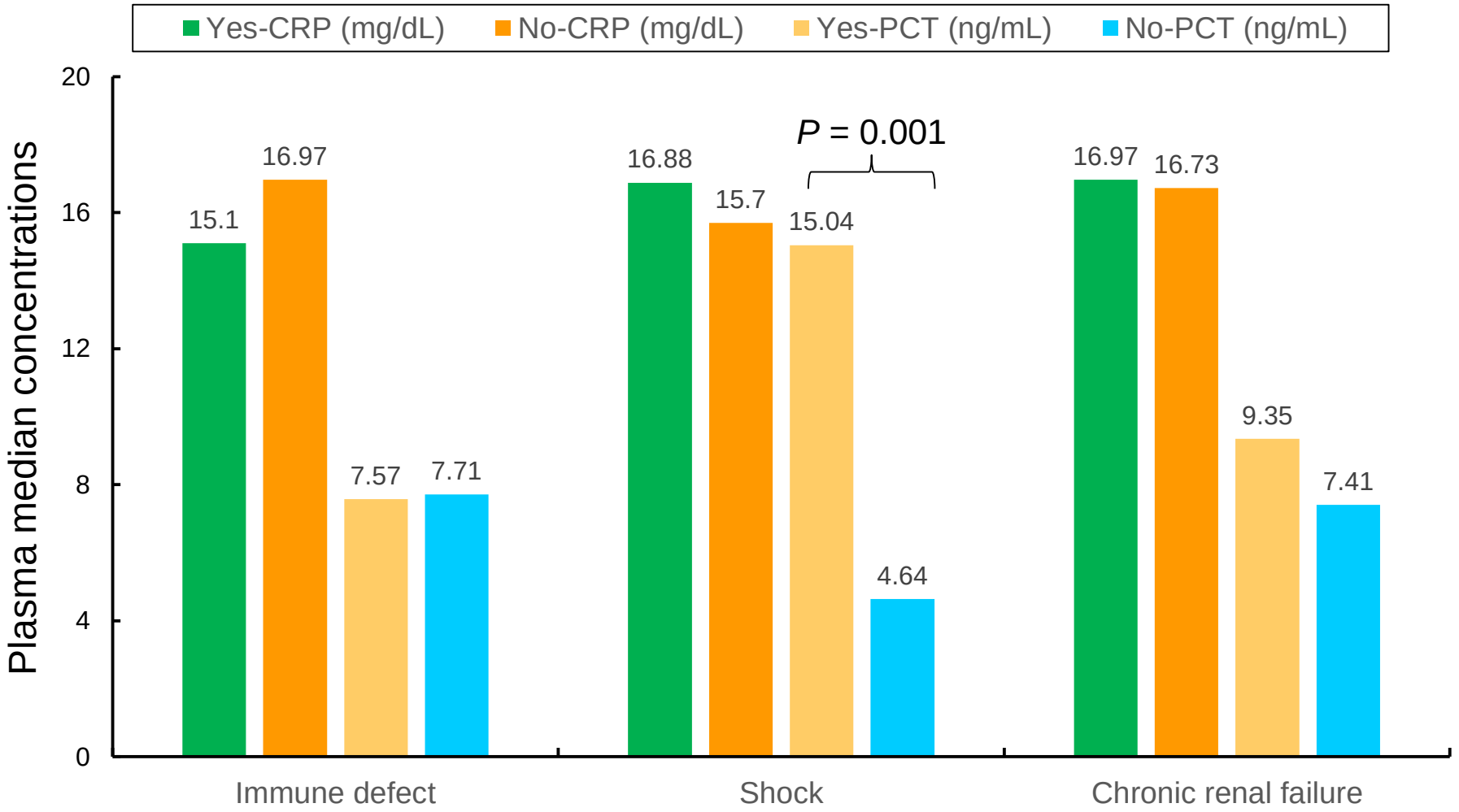
Long-term H/D: ***not*** a factor contributing to ↑ plasma [PCT]

Fig. 3. Cumulative mortality rates in high and low plasma procalcitonin (PCT) groups among intensive care unit (ICU) patients with monomicrobial Gram-negative bacteremia.

Limitations in plasma [PCT] interpretation

- Significance of ileus of different degree (ileus 也會引起腸道的發炎; 但臨床上, ileus 的定義偏模糊, 且大多數 sepsis/septicemia, 不管有沒有合併菌血症, 經常也會合併程度不等的 ileus ….) ?
- Immune defective subjects 是依照**國際的定義**做挑選; 因此, 本研究未將 ESRD receiving long-term H/D 歸類為 immunocompromised hosts; 但部分醫師或學者, 認為 long-standing H/D recipients, 應該也有 defective immunity ……
- ARDS, ECMO use, bacterial co-infections in **virus** pneumonitis: ↑↑ plasma [PCT] (**>1.0** ng/mL).
- 未來可以做更大規模的研究, 蒐集更多定義清楚的 **cases** 來做前瞻性分析 (並非使用資料庫來撈 data).

Gram (+) bacteria 革蘭氏陽性菌 (*n*=132)



T2P, median (IQR), hours	Yes	[n=23] 44 (17.5, 50.5)	[n=88] 38 (19, 57)	[n=41] 32.5 (14, 53.75)
	No	[n=109] 40 (18, 58)	[n=44] 42 (16.25, 58.75)	[n=91] 43 (19, 57)

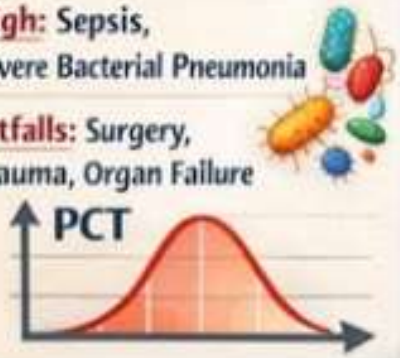
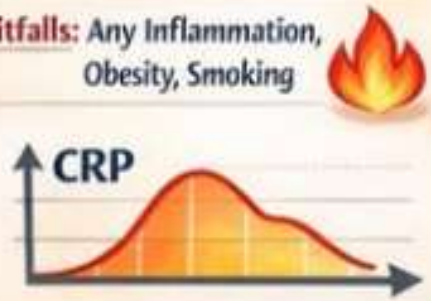
Plasma PCT concentration ranges, in other miscellaneous infections

- Pulmonary *Aspergillus* spp. infections ?
- *Cryptococcus* infections ?
- *M. tuberculosis* infections ?
- Leptospirosis (Weil's disease) ?

Top Gun (Tom Cruise, in 1986)

Procalcitonin (PCT) vs CRP vs ESR

Comparing Diagnostic Markers

Procalcitonin (PCT)	CRP (C-Reactive Protein)	ESR (Erythrocyte Sedimentation Rate)
• Bacterial Infection & Sepsis	• Acute Inflammation	• Chronic Inflammation
• Guiding Antibiotics	• Infection, Autoimmune, Injury	• Temporal Arteritis, PMR
• Rises 3 h, Peaks ~24h	• Rises 6–12h, Peaks 24–48h	• Rises 24–48h, Stays High Weeks
• Falls Fast	• Falls Over Days	• Slower to Fall
• More Specific for Bacterial	• Sensitive, Good for Monitoring	• Least Specific
High: Sepsis, Severe Bacterial Pneumonia	High: Infection, Autoimmune Flare	High: TB, Chronic Disease, Malignancy
Pitfalls: Surgery, Trauma, Organ Failure	Pitfalls: Any Inflammation, Obesity, Smoking	Pitfalls: Anemia, Older Age, Kidney Disease
		
High: Sepsis, Surgery, Trauma, Organ Failure	High: Infection, Autoimmune Flare Obesity, Smoking	High: TB, Chronic Disease, Malignancy Anemia, Older Age, Kidney Disease
PCT: Best for Bacterial & Sepsis	CRP: Broad Inflammation Marker	ESR: Chronic & Inflammatory Conditions

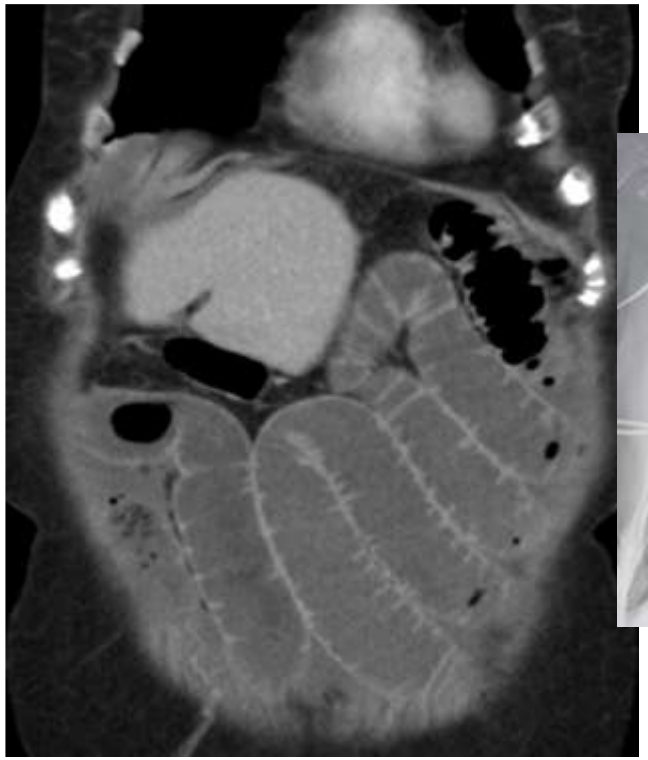
$T_{1/2}$ (PCT): 22-26 hours

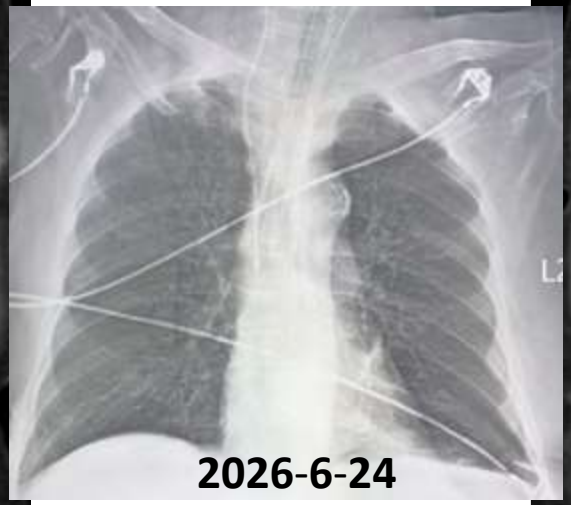
$T_{1/2}$ (**CRP**): about **20** hours

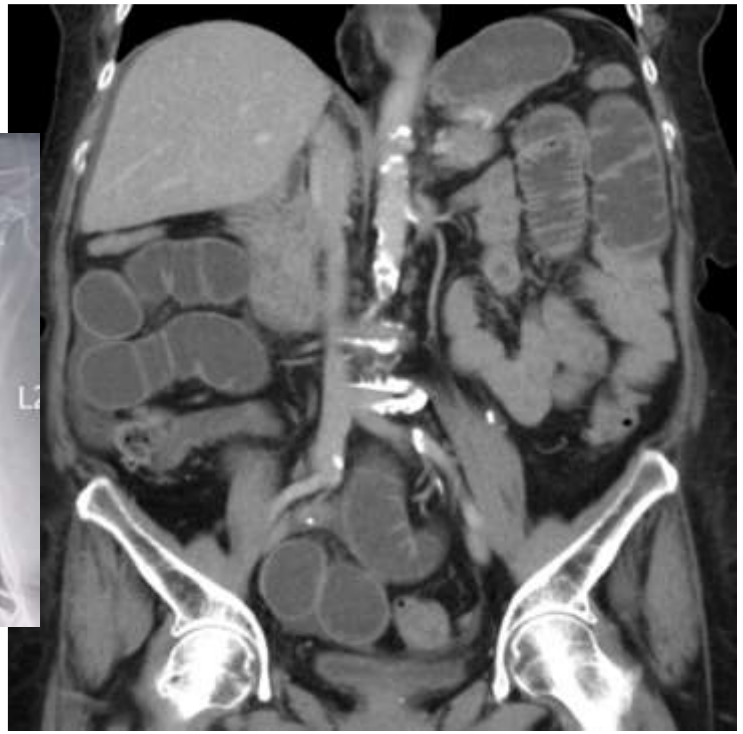
(and: monitor sepsis tx **response**)

Case 1: A 71-year-old female patient, with DM and receiving C/S 40 years ago, was admitted on 6/10 because of small bowel ileus. Due to suspicious sepsis with acute kidney injury, & high plasma [PCT], parenteral piperacillin-tazobactam was administered since **6/12** …. (1)

Plasma [PCT] (on **6/12**): 97.09 ng/mL >>>> (**6/23**): 48.22 ng/mL. **B/C** (**6/23 11pm**): ***E. coli*** (T2P: **12** hours)







Case 1: This 71-year-old female patient had the diagnosis of small bowel ileus. However, her cause of ileus was not conclusive at general ward. Sudden-onset aggravating lower abdominal pain, dyspnea, & conscious change developed on **6/23** night. A high plasma [**PCT**] was also recorded on **6/23** …. (2)

Operation findings (**6/24** night)

1. A segmental small bowel (40 cm from the ileocecal valve) ischemic change, with multiple gangrene change perforation; distal ileum almost autoamputation.
2. Resected the 50 cm small bowel ---> creating distal ileum stomy. Turbid ascites ~3000 cc

SID	開單日	採收日	醫師	報告日期	報告時間	檢體別	備註
B60624643135	115.06.23	115.06.24		115.06.24	19:19:42	Blood	First report R CVP neck感染陽性日期:115.06.24,時間=10:56:21
B60624643135	115.06.23	115.06.24		115.06.26	09:49:07	Blood	R CVP neck感染陽性日期:115.06.24,時間=10:56:21 Final report

培養別： Blood Culture 13016 Culture Reprot有長菌株數:1 株 檢體別：Blood

sno	菌種名稱	價數	Colony	報告日期	報告時間
1	Escherichia coli			115.06.26	09:38:18

sno	抗生素名稱	簡稱	1	MIC	2	MIC	3	MIC	4	MIC
01	Ampicillin/sulbactam	SAM-	R	>=32						
02	Piperacillin/Tazobactam	TZP	S	8						
03	Cefazolin (other)	CZ03	R	>=64						
04	Cefmetazole	CMZ	S	8						
05	Cefotaxime	CFT	R	4						
06	Ceftazidime	TAZ	S	4						
07	Cefepime	CPE	S	<=1						
08	Ertapenem	ETP	S	<=0.5						
09	Imipenem	IMI	S	<=0.25						
10	Meropenem	MER	S	<=0.25						
11	Amikacin	AN	S	<=2						
12	Gentamicin	GM	R	>=16						
13	Ciprofloxacin	CP	R	1						
14	Levofloxacin	LEV	I	1						
15	Colistin	CS	I	<=0.5						
16	Trimethoprim/Sulfamethoxazole	SXT	R	>=320						

Mortality on **6/26** (Friday), 8am.

ESBL-producing ***E. coli*** bacteremia, which source could be adequately treated with **piperacillin/tazobactam** ?

出生年月日：1953-02-20　性別：男　資料範圍：2026-08-13至2026-08-19

病歷號：M22692　入院日期：2026-07-21　床位號：03G061

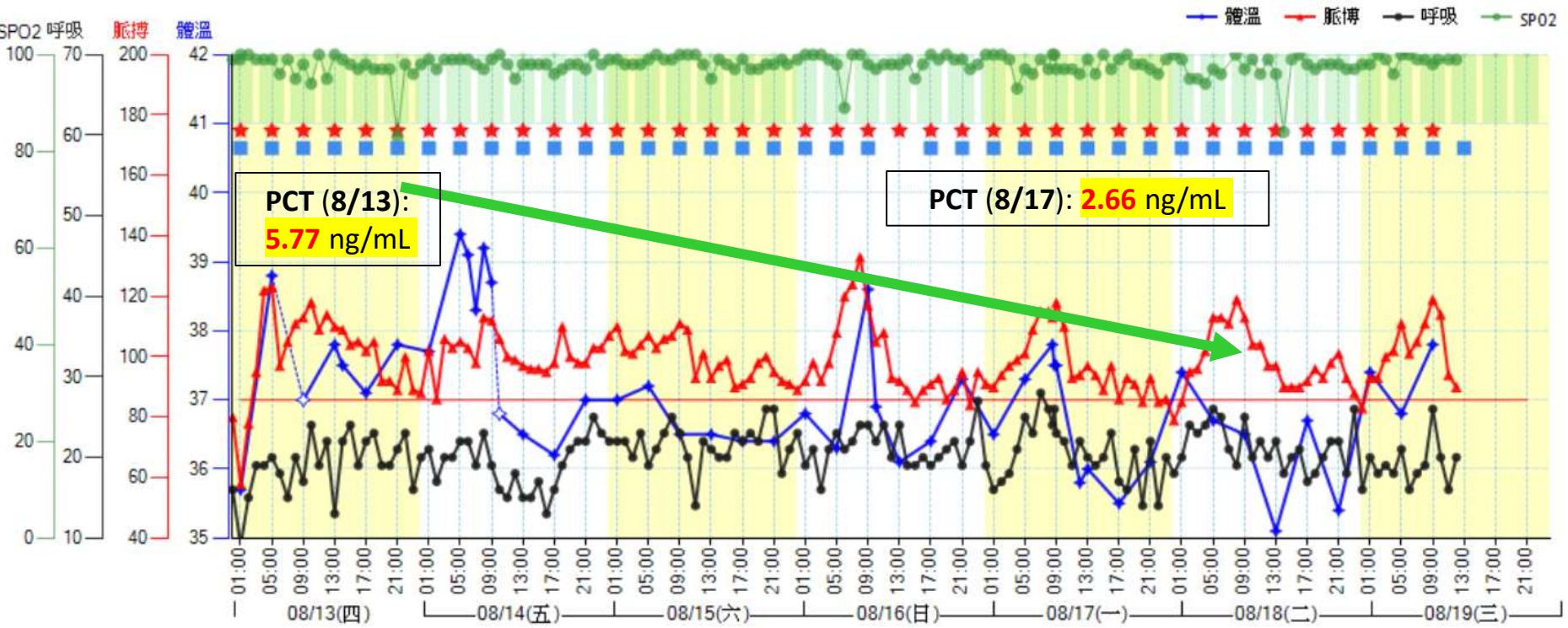
主診斷：Dissection Of Unspecified Site Of Aorta　編輯

科別：心臟血管外科　主治醫師姓名：簡修洵

Case 2: A 74-year-old male patient, with DAA s/p aortic stent deployment, suffered from repeated GI hemorrhage ….

查詢

特殊註記：■：轉床 ■：手術 ■：抗生素 ★：ICU/RCC (前4項系統自動帶入) ■：重大處置 ■：重大檢查 ▲：急救 ■：其它　查詢內容，請點選圖表上方【註記點】

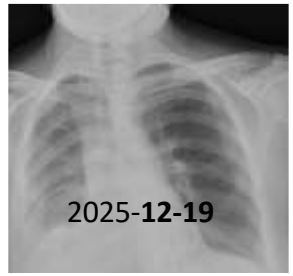


入院日數	23	24	25	26	27	28	
術後日數	23	24	25	26	27	28	29
加護病房日數	22	23	24	25	26	27	28
血壓	83 / 46 mmHg more	118 / 60 mmHg more	112 / 57 mmHg more	140 / 66 mmHg more	130 / 68 mmHg more	133 / 71 mmHg more	127 / 70 mmHg more
Daptomycin (Cubicin) 500mg/vial $				D1	D2	D3	D4
Cefiderocol (Fetroja) 1g/vial $@				D1	D2	D3	D4

Case 3: A 38-year-old female, seizure since neonatum, suffered from Rt empyema (*Streptococcus* group G) s/p VATS decortication (11/27); ceftriaxone was used, but right lung consolidations worsen (12/01) ….. MBD on 12/20

New sputum culture: grew wild-type *Enterobacter cloacae* complex (CMZ-R, but CTX/CRO-S) on 12/02 >>>> a potential **AmpC** hyperproducer. Is antibiotic regimen needed for adjustment

sno	菌種名稱		備數	Colony	報告日期	報告時間
1	Enterobacter cloacae complex		Moderate		114.12.05	09:44:08
sno	抗生素名稱	簡稱	1	MIC	2 MIC	3 MIC	4 MIC
01	Piperacillin/Tazobactam	TZP	S	<=4			
02	Cefazolin	CFZ	R	>=64			
03	Cefmetazole	CMZ	R	32			
04	Cefotaxime	CFT	S	<=1			
05	Ceftazidime	TAZ	S	<=1			
06	Cefepime	CPE	S	<=1			
07	Ertapenem	ETP	S	<=0.5			
08	Imipenem	IMI	S	<=0.25			



Rocephin (11/26~12/05) → **Cefepime** (12/06~)

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 02 September 2025
DOI 10.3389/fmed.2025.1597047

Timing of antibiotic initiation in sepsis and neutropenic fever

Jenny Gretland[1†], Sigrun Sjømæling[1†], Knut Anders Mosevoll[2‡] and Håkon Reikvam[2,3‡*]

Front Med (Lausanne) 2025 Sep 2:**12**:1597047 Gretland J et al

[1]Faculty of Medicine, University of Bergen, Bergen, Norway, [2]Department of Medicine, Haukeland University Hospital, Bergen, Norway, [3]K.G. Jebsen Center for Myeloid Blood Cancer, Department of Clinical Science, University of Bergen, Norway

(**Abx** use, within **3** h vs. beyond **3** h)

TABLE 1c Presents studies using the Sepsis 1/2 definitions, comparing outcomes between time to first antibiotic (TTFA) within 3 h versus beyond 3 h.

References	Sample size	Patient outcome	Does the study differentiate between sepsis, severe sepsis, and septic shock?	Significant association between TTFA and outcome?	Median time to AB (h)	Details, OR
Seymour et al. RCS/2017 (36)	49,331	In-hospital mortality	Yes, studies severe sepsis and SSh	Yes	0.95 (0.35–1.95)	< 3 h vs 3–12 h: OR 1.14 (95% CI 1.06–1.22; $P = 0.001$)
Peimelli et al. RCS/2018 (34)*	5,672	In-hospital mortality	Yes, studies severe sepsis or SSh	Yes	ND	Graphic display of effect measure.
Ko et al. PCS/2020 (47)	2,250	In-hospital mortality	Yes, studies SSh	Yes	2.29 (1.42–3.5)	> 3 h => OR 1.324 (95% CI 1.148–1.529; $P = 0.001$)
Londoño et al PCS/2018 (48)	884	In-hospital mortality	No	Yes	4.0 (2–7)	Reduction in mortality of 21% ($P = 0.045$)
Rhee et al. RCS/2019 (13)*	951	In-hospital mortality	Yes, studies severe sepsis and SSh	Yes	ND	aOR 1.94 (95% CI 1.04–3.62, $P = 0.038$)
Joo et al. RCS/2014 (49)	591	In-hospital mortality	Yes, studies severe sepsis and SSh	Yes	1.9 (1.4–2.4)	aOR 0.54 (95% CI 0.34–0.87; $P = 0.01$)
Gaieski et al. RCS/2010 (21)	261	In-hospital mortality	Yes, studies severe sepsis and SSh	No	1.98 (1.27–3.2)	Time from ED triage and TTFA: No significant association.

*Unspecified sepsis definition. ED, emergency department; ND, not demonstrated; SSh, septic shock.

∴ Most studies supported survival benefits **Abx** use <3 h

(**Abx** use, within **6** h vs. beyond **6** h)

TABLE 1d Presents studies using the Sepsis 1/2 definitions, comparing outcomes between time to first antibiotic (TTFA) within 6 h versus beyond 6 h and other time points studied.

References	Sample size	Patient outcome	Does the study differentiate between sepsis, severe sepsis, and septic shock?	Significant association between TTFA and outcome?	Median time to AB (h)	Details, OR
Ferrer et al. PCS/2009 (13)*	2,796	In-hospital mortality	Yes, studies severe sepsis and SSh	Yes	ND	Broad-spectrum AB < 1 h vs. no AB < 6 h: aOR 0.67 (95% CI, 0.50–0.90; $P = 0.008$)
Schinkel et al. RCS/2021 (51)	2,672	28 days mortality	No	Yes	1.6 (0.6–2.1)	Antibiotics received in a prehospital setting: OR = 0.07 (95% CI, 0.01–0.79; $P = 0.031$)
Puskarich et al. PCS/2011 (20)	291	In-hospital mortality	Yes, studies SSh	Yes, before and after shock recognition	1.92 (1.1–2.92)	No hourly significant association between mortality and TTFA within the first 6 h. TTFA before and after shock recognition: aOR 2.49 (95% CI 1.7–5.74)
Gaieski et al. RCS/2010 (21)	261	In-hospital mortality	Yes, studies severe sepsis and SSh	No	1.98 (1.27–3.2)	Time from ED triage and TTFA at different hourly cutoffs: No significant association, except < 1 h <.
Wisdom et al. RCS/2015 (30)	220	In-hospital mortality	Yes, studies sepsis and severe sepsis	No	3.5 (1.7–6.6)	Uncomplicated sepsis: No association between increased delay to antibiotics and mortality. Severe sepsis: Increased mortality with delays in TTFA with more than 6 h compared with TTFA within 1 h: HR 2.25 (95% CI 0.91–5.59; $P = 0.08$)
Andersson et al. RCS/2019 (32)	90	28 days mortality	Yes, studies severe sepsis and SSh	Yes	ND	Studied the effect of 1st dose antibiotic treatment given < 1 h, and 2nd dose with less than 25% delay. OR 0.096 (95% CI 0.011–0.846; $P = 0.035$)

*Unspecified sepsis definition. AB, antibiotic therapy; ED, emergency department; ND, not demonstrated; SSh, septic shock.

Support <**6** h

Adjusted hazard ratio (aHR) for **Abx** use between <**6** h vs. <**1** h: **2.25** (95% CI, 0.91–5.59; $P = 0.08$)

REVIEW
Korean J Intern Med 2025;40:725-733
https://doi.org/10.3904/kjim.2025.037

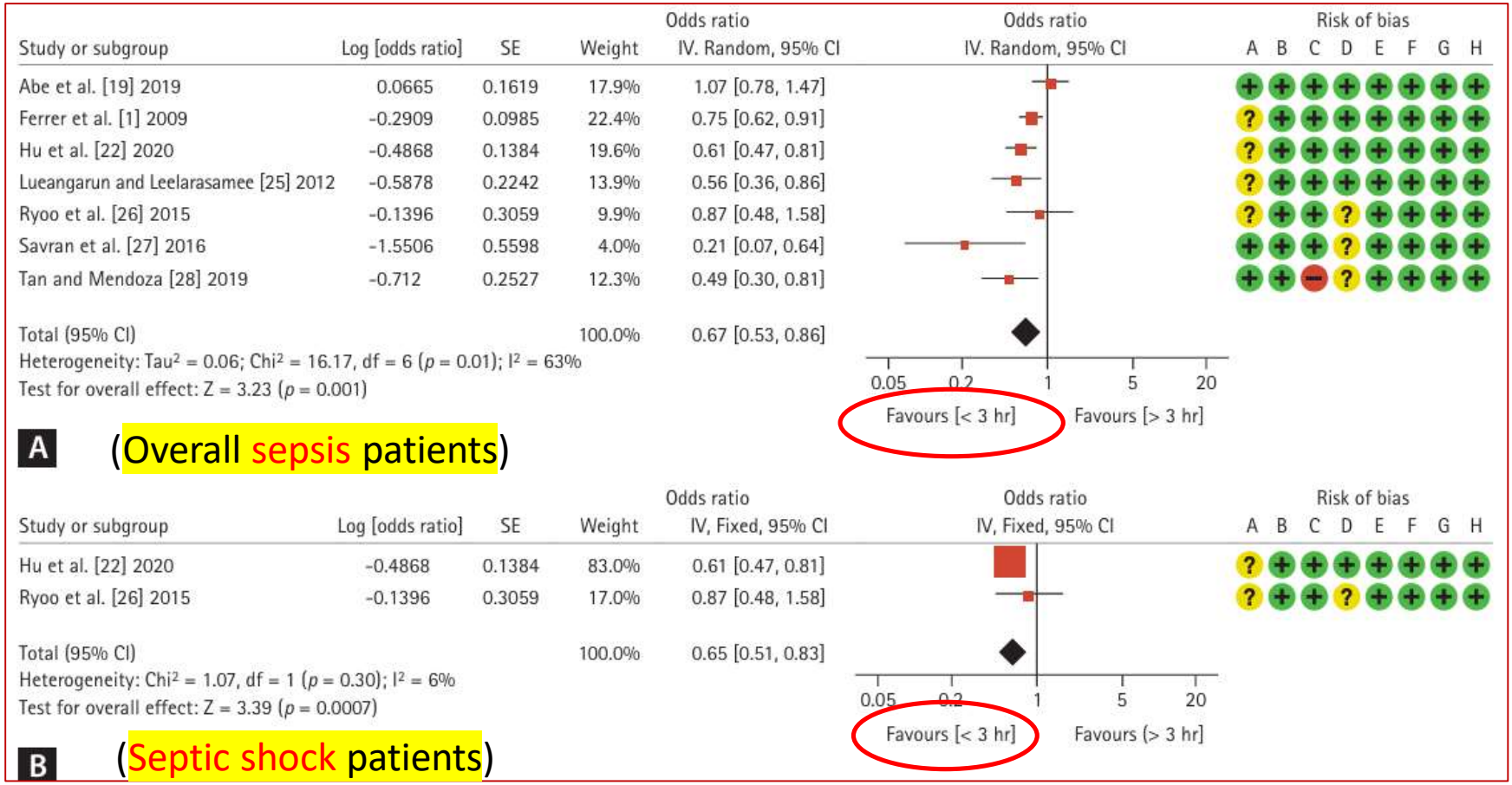
KJIM

Appropriate timing of antibiotic initiation in patients with sepsis or septic shock: a systematic review and meta-analysis

Nam Su Ku[1,*], Yongseop Lee[1,*], and Dae Won Park[2]

Sepsis 病人, 於三小時內, 接受合適的抗生素治療.最能夠改善病人的 30 天死亡率

Korean J Intern Med 2025 Sep;**40**(5):725-33 Su NS et al



Time to Antibiotics

Time to Antibiotics

Recommendations

12. For adults with possible septic shock or a high likelihood for sepsis, we **recommend** administering antimicrobials immediately, ideally within one hour of recognition. (SSC 2026 April: 不變)

Strong recommendation, low quality of evidence (septic shock)

Strong recommendation, very low quality of evidence (sepsis without shock)

13. For adults with possible sepsis without shock, we **recommend** rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness.

Best practice statement.

Remarks:

14. For adults with possible sepsis without shock, we suggest a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 hours from the time when sepsis was first recognized.

Weak recommendation, very low quality of evidence.

15. For adults with a low likelihood of infection and without shock, we suggest deferring antimicrobials while continuing to closely monitor the patient.

Weak recommendation, very low quality of evidence.

(particularly for patients with **MDR/XDR-GNB**, **fungal** infections)

Each additional hour of time from ER arrival to administration of antimicrobials was associated with **1.09** increased odds of in-hospital mortality.

Whenever possible, an initiation of antimicrobial therapy should be completed within **3 hours** of presentation, so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood of sepsis is thought to be high.

The **mortality** reduction associated with early antimicrobials appears **strongest** in patients with septic shock, while weaker associations in patients without septic shock (rapid assessment of infectious vs. non-infectious causes is needed when possible).

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial

Evelien de Jong, Jos A van Oers, Albertus Beishuizen, Piet Vos, Wytze J Vermeijden, Lenneke E Haas, Bert G Loef, Tom Dormans, Gertrude C van Melsen, Yvette C Kluiters, Hans Kemperman, Maarten J van den Elsen, Jeroen A Schouten, Jörn O Streefkerk, Hans G Krabbe, Hans Kieft, Georg H Kluge, Veerle C van Dam, Joost van Pelt, Laura Bormans, Martine Bokelman Otten, Auke C Reidinga, Henrik Endeman, Jos W Twisk, Ewoudt M W van de Garde, Anne Marie G A de Smet, Jozef Kesecioglu, Armand R Girbes, Maarten W Nijsten, Dylan W de Lange

Test the safety of discontinuing Abx when the plasma [PCT] (1) decreases by ≥80% of its peak levels, or (2) is below 0.5 ng/mL

Lancet Infect Dis 2016 Jul;**16**(7):819-27 de Jong E et al

The reduction of antibiotics using [PCT] as guidance tool was in association with a significant **decrease** in mortality. Use of plasma **PCT** concentrations might lead to more adequate diagnosis and treatment in **ICU** pts with **sepsis**, the cornerstones of antibiotic stewardship.

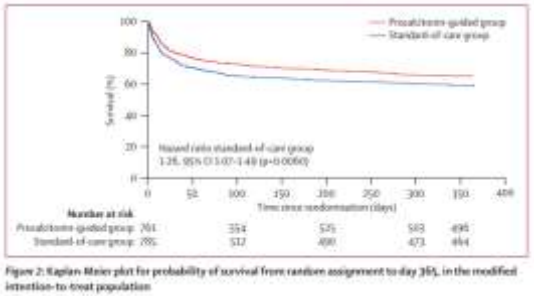
Procalcitonin group (*n*=761)

(**1**) Median Abx consumption: 7.5 DDD (IQR 4·0–12·7)

(**2**) Median tx length: 5 days (3–9 days)

(**3**) Day 28 mortality: 20%

All parameters, $P < 0.05$



Standard-of-care group (*n*=738)

(**1**) Median Abx consumption: 9.3 DDD (IQR 5·0–16·6)

(**2**) Median tx length: 7 days (4–11 days)

(**3**) Day 28 mortality: 25%

Case 4: A 54-year-old man, with (**1**) DM, (**2**) ESRD under t.i.w H/D, received (**3**) recent MI s/p CABG in May 2026. His postoperative course was complicated by multiple infection episodes …..

SID	開單日	簽收日	醫師	報告日期	報告時間	檢體別	備註
B60603623259	115.06.03	115.06.03		115.06.04	00:31:24	Blood	
B60603623259	115.06.03	115.06.03		115.06.04	02:02:34	Blood	

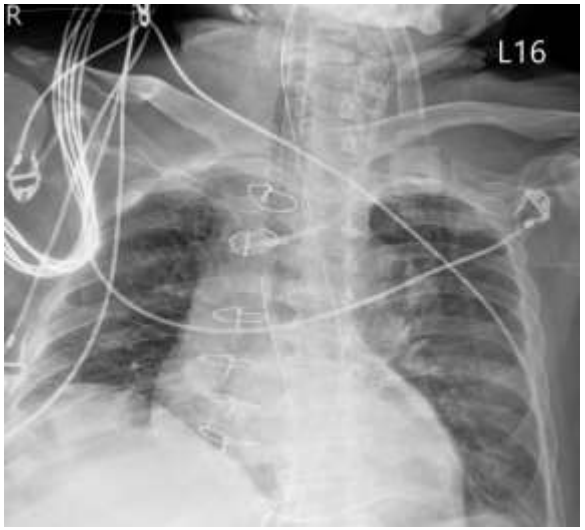
No	時間	檢驗項目	結果值		參考值範圍	單位
		[血清學檢查]				
1	00:31:24	Procalcitonin(PCT)	11.01	H	<0.05	ng/mL
2	00:31:24	Cortisol	32.8			ug/dL
3	02:02:34	TSH	0.2502	L	0.35 - 4.94	uIU/mL
4	02:02:34	Free-T4	1.01		0.70 - 1.48	ng/dL

Despite **vanco** + **pip/tazo** tx (6/07~) and **CRRT** support …. ***no*** significant plasma [**PCT**]↓

SID	開單日	簽收日	醫師	報告日期	報告時間	檢體別	備註
B60609964436	115.06.09	115.06.09		115.06.09	06:20:35	Blood	

No	時間	檢驗項目	結果值		參考值範圍	單位
		[血清學檢查]				
1	06:20:35	Procalcitonin(PCT)	9.50	H	<0.05	ng/mL

Repeated revisions of central venous lines have been done ….



Final answer: VR-***E. faecium*** **BSI**

SID	開單日	簽收日	醫師	報告日期	報告時間	檢體別	備註
B60609629313	115.06.08	115.06.09		115.06.10	08:34:34	Blood	First report Right neck CVP導管陽性日期:115.06.09,時間=23:26:23
B60609629313	115.06.08	115.06.09		115.06.12	09:29:41	Blood	Right neck CVP導管陽性日期:115.06.09,時間=23:26:23 Second report,VRE. 請執行導管移除

培養別： Blood Culture 13016 Culture Report有長菌檢數:1 株 檢體別： Blood

sno	菌種名稱	備數	Colony	報告日期	報告時間
1	Enterococcus faecium(VRE)			115.06.12	09:16:41

sno	抗生素名稱	簡稱	1	MIC	2	MIC	3	MIC	4	MIC
01	Penicillin G	PENG	R	>=64						
02	Gentamicin High Level (synergy)	GMS	S	SYN-S						
03	Streptomycin High Level (synergy)	STS	S	SYN-S						
04	Erythromycin	E	S	<=0.25						
05	Linezolid	LNZ	S	2						
06	Teicoplanin	TPN	I	16						
07	Vancomycin	VA	R	>=32						

Right neck CVP導管陽性日期:115.06.09,時間=23:26:23
Second report,VRE. 請執行導管移除

Microbiological and clinical characteristics of vancomycin-resistant *Enterococcus faecium* bacteraemia in Taiwan: implication of sequence type for prognosis (during 2003-2010, at **NTUH**)

Ching-Lan Lu[1], Yu-Chung Chuang[2], Hao-Chun Chang[3], Yee-Chun Chen[2], Jann-Tay Wang[2]* and Shan-Chwen Chang[2]

J Antimicrob Chemother 2012; **67**: 2243–2249

VR-*E. faecium* BSI

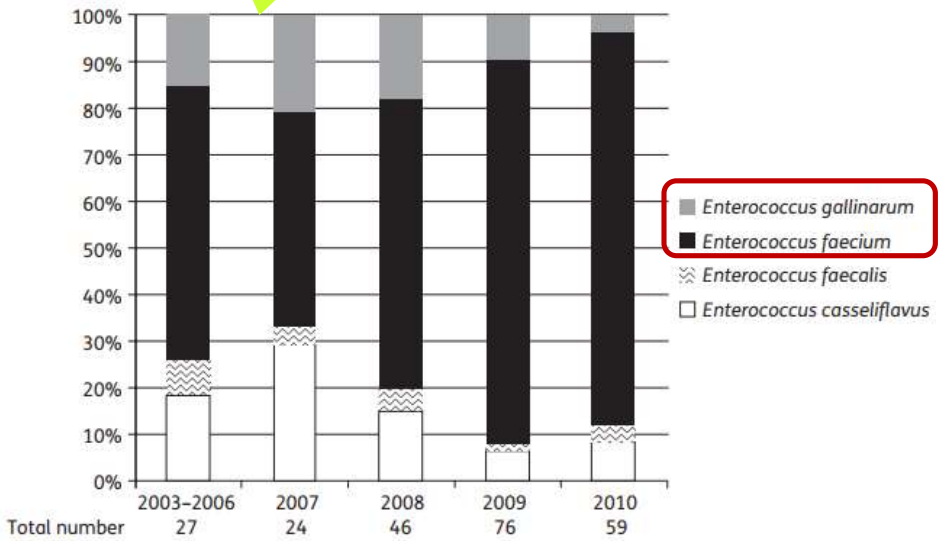


Figure 1. Species distribution of 232 blood VRE isolates from 2003 to 2010.

Figure 2. Resistance rate to vancomycin of blood enterococcal isolates from 2003 to 2010.

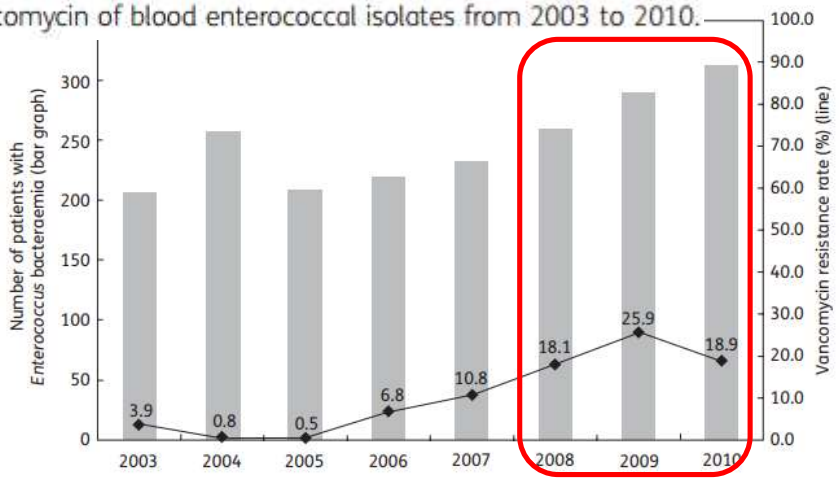


Table 3. Risk factors for all-cause 14 and 28 day mortality of patients with VREfm bacteraemia by multivariate analysis

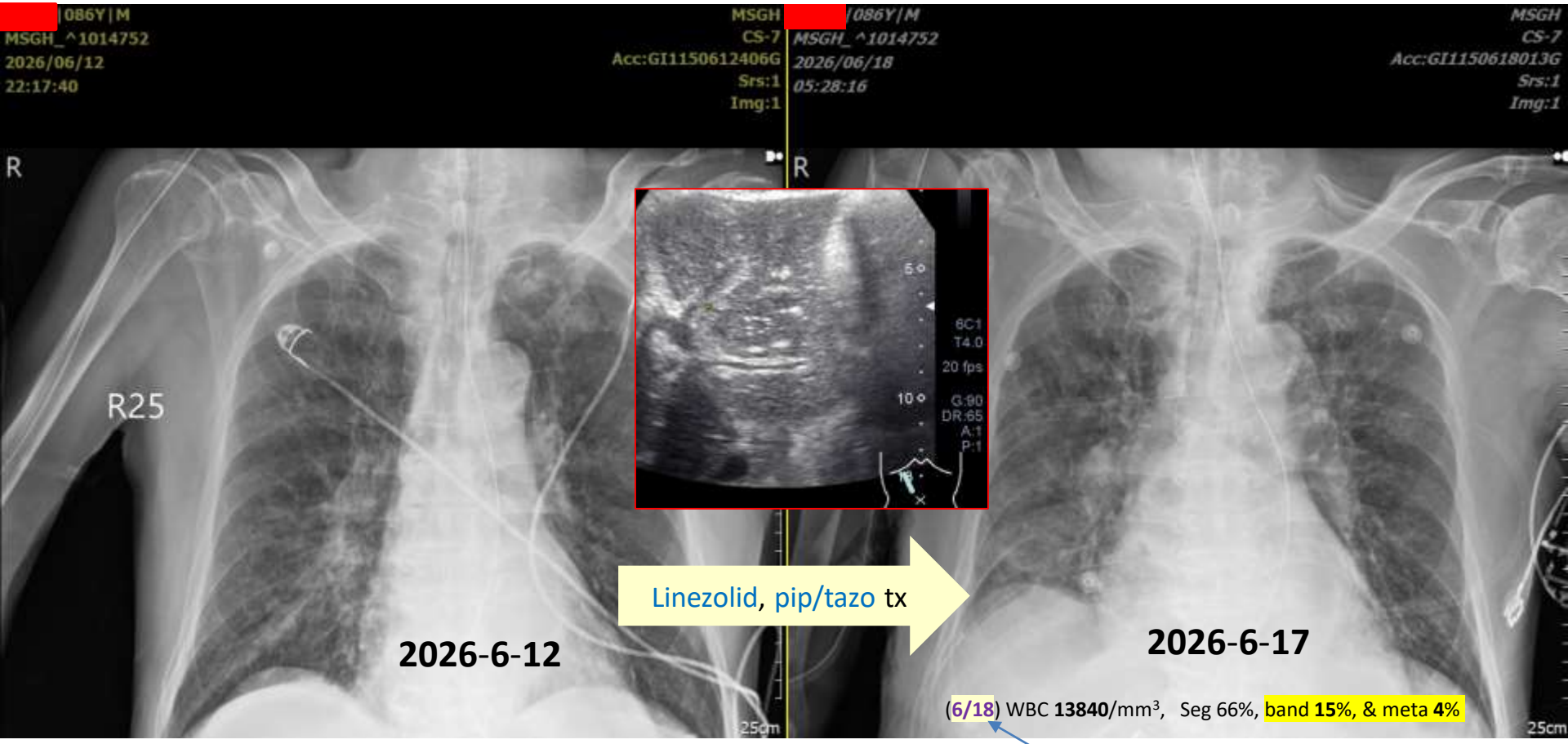
	OR	*P* value	95% CI
14 day mortality[a]			
received appropriate treatment	0.31	0.037	0.10–0.96
received immunosuppressant agents	6.66	<0.001	2.30–19.32
high Charlson comorbidity index	1.24	0.038	1.01–1.51
septic shock	12.87	<0.001	3.79–46.69
ST414 strain	0.24	0.044	0.06–0.96
28 day mortality[b]			
longer prior hospital stay	1.02	0.015	1.00–1.04
thrombocytopenia	3.23	0.007	1.39–7.54
septic shock	9.08	<0.001	3.64–22.65

[a]Goodness of fit for 14 day mortality: deviance goodness-of-fit test $P=0.5985$ >0.05 (df=55); Pearson goodness-of-fit test $P=0.4728$ >0.05 (df=55); Hosmer and Lemeshow goodness-of-fit test $P=0.6611$ >0.05 (df=8).
[b]Goodness of fit for 28 day mortality: deviance goodness-of-fit test $P=0.3543$ >0.05 (df=115); Pearson goodness-of-fit test $P=0.2531$ >0.05 (df=115); Hosmer and Lemeshow goodness-of-fit test $P=0.6749$ >0.05 (df=8).

In this VRE*fm* bacteremia (*n* = 149) study ---

1. Primary bacteremia, **76.5%**; polymicrobial BSI, 38.4%, with sepsis presentation of **85.9%**
2. Charlson index score, **4.3** ± 0.2; **Vancomycin**, **teicoplainin** exposure (within 14 days), **36.9%** and **11.4%**, respectively.
3. Day 14 & 28 mortality rate, **48.3%** and **59.7%**, respectively
4. Linezolid therapy achieved survival, **>50%** (much better daptomycin, only 20-23% survival rate), an important **modifiable** factor in sepsis

Case 5: An 85-year-old elderly patient, with underlying GIST and chronic kidney disease (stage 3), was admitted to MICU in **May** 2026 because of **AMI** involving RCA. Then **MRSA** pneumonia developed with improvement later, but: recurrent clinical deterioration since **6/18** …..

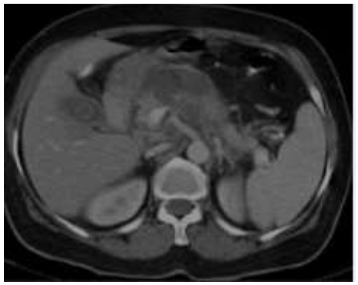


Although his MRSA pneumonia improved after appropriate therapy, his urine culture grew ***C. albicans***, and bronchoscopy washing fluid culture also grew ***C. albicans***. >>> His blood culture on **6/18** 11am also grew ***Candida albicans***. [**PCT**] (on **6/12**, stable): **2.03** ng/mL, & (**6/18**): **5.34** ng/mL (↑).

Risk factors for *Invasive Candidiasis*

Blue: surgery. Red: Medical aspect

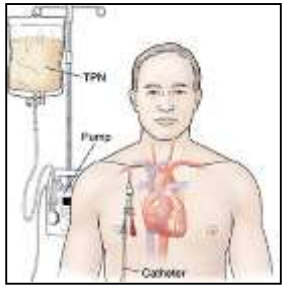
From: ***IDSA*** 2016 Guidelines



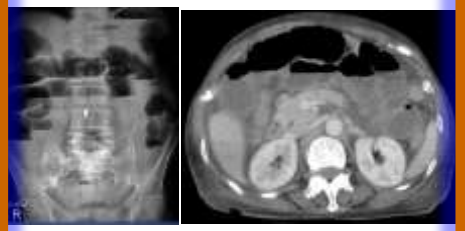
Necrotizing pancreatitis

Hemodialysis

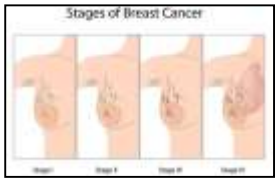
Use of CVCs



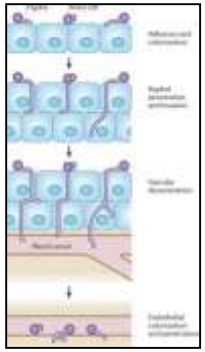
Total parenteral nutrition (**TPN**) infusion



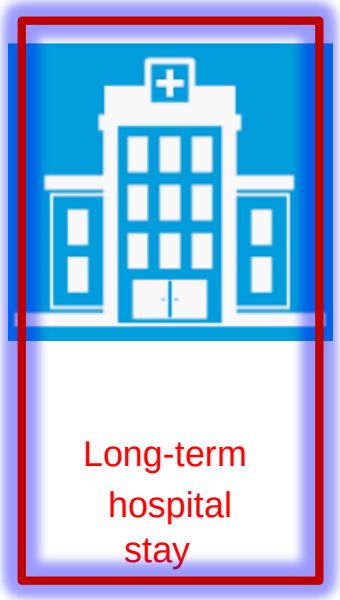
Paralytic ileus



Immunosuppressed hosts

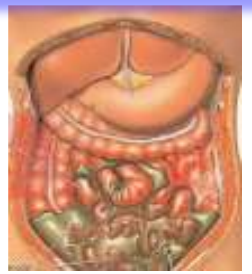


Multifocal *Candida* colonizations



Long-term hospital stay

Exposure to **ESCs**, **carbapenem**



Recent **abdominal** surgery

總而言之: 內科系病人若得到 ***invasive candidiasis***, 通常都**很難**早期發現!

Intra-abdominal *Candidiasis* (IAC): The Importance of Early Source Control, and start Antifungal Treatment

PLoS One 2016;**11**:e0153247 Vergidis P et al

Table 5. Predictors of 100-day mortality for subjects with IAC stemming from GI tract sources.

Parameter	Non-survivors (n = 26)	Survivors (n = 77)	Univariate OR (95% CI)	Univariate *P* value	Multivariate OR (95% CI)	Multivariate *P* value
Age, median (interquartile range)	68 (58–77)	58 (46–68)	1.04 (1.01–1.08)	0.01	1.04 (1.01–1.08)	0.018
Male	15 (58)	32 (42)	1.92 (0.78–4.72)	0.16		
Solid organ transplant	3 (12)	4 (5)	2.38 (0.50–11.43)	0.28		
Obesity (BMI >30)	11 (42)	18 (23)	21.84 (0.67–5.02)	0.07	...	...
Healthcare-associated disease	20 (77)	61 (79)	0.87 (0.30–2.54)	0.81		
APACHEII score	17 (7–27)	16 (5–29)	1.04 (0.94–1.14)	0.47		
Septic shock	6 (23)	11 (14)	1.8 (0.59–5.48)	0.30		
Perforation	19 (73)	51 (66)	1.38 (0.52–3.71)	0.52		
Presence of abscess	11 (42)	48 (62)	0.44 (0.18–1.09)	0.08	0.36 (0.13–0.96)	0.042
Bacterial co-infection	16 (62)	57 (74)	0.56 (0.22–1.44)	0.23		
C. glabrata infection	7 (27)	23 (30)	0.86 (0.32–2.34)	0.78		
Candidemia	0/19	3/57 (5)		0.57		
Surgical intervention	19 (73)	50 (65)	1.47 (0.55–3.92)	0.45		
Surgical intervention (within 5d)	15 (58)	42 (55)	1.55 (0.63–3.81)	0.78		
Source control intervention (within 5d)	17 (65)	63 (82)	0.49 (0.20–1.22)	0.09	...	...
Antifungal treatment (within 5d)	13 (50)	56 (73)	0.38 (0.15–0.94)	0.04	0.36 (0.13–0.96)	0.042
Infectious disease consultation	6 (23)	28 (36)	0.53 (0.19–1.46)	0.22		

← 3/76 (**4**%)

The most relevant diagnostic tests, for *invasive Candidiasis* (IC)/infection

J Hosp Infect 2017 (Review) Oleary RA et al; & ***NEJM*** 2015 (Review)

Diagnostic test	Advantages	Limitations
Culture	Gold standard But: required for anti-fungal susceptibility testing (**sensitivity**, 21-71%)	# Results take time # Some infecting organisms do ***not*** grow on cultures # Insensitive, may identify only 50% of all patients with **IC**
Histology	Also gold standard Broad categories of potential pathogens can be differentiated	# Invasive procedure(s) # Sensitivity depends on proper sample collection # It has limited specificity to identify genus and species level
Antigen detection: **(1,3)-β-D-glucan** (**BDG**) assay (serum, BAL, CSF, also for *Aspergillus* spp.)	**Serial** surveillance of at-risk patients may help early identification of **IC,** and start pre-emptive therapy (***except*** for hematologic malignancy patients in whom false-positive results are common); **sensitivity**, 65-100%, **specificity**, 31-79%, dependent on cutoff level, numbers of (+) samples. May be used for monitoring response to therapy.	# But: **non**-specific, **pan**-fungal screening test. In fact, **BDG** is a cell wall constituent of ***Candida*** spp., ***Aspergillus*** spp., *Pneumocystis jirovecil* and several other fungi. # Repeated positive results are required for dx. # False –positive tests, could be seen in : certain **hemodialysis** membranes, IVIG, Augmentin® therapy, fresh frozen plasma (**FFP**), or surgical gauze product use, **GNB** (>> **GPC**)-**BSI**, etc (***E. coli***, ***P. aeruginosa*** >> ***S. aureus***)

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Open Forum Infectious Diseases
MAJOR ARTICLE

Stewardship-Guided T2Candida Testing Shortens Time to Antifungal Treatment and Reduces Antifungal Usage Among Medical Intensive Care Unit Patients With Septic Shock

(**14**% with *Candida* score ≥3)

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Table 3. Diagnostic Performance of T2Candida for Proven and Probable IC[a]

Performance Characteristics	Proven IC	Proven and Probable IC
Sensitivity, %	71.4	77.8
Specificity, %	93.9	95.2
LR^+	11.8	16.2
LR^-	0.3	0.23
Prevalence, %	4.5	5.8
PPV, %	35.7	50
NPV, %	98.6	98.6

Abbreviations: LR^+, positive likelihood ratio; LR^-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

[a]Assumes probable IC cases to be true positives that were missed by blood culture.

Table 4. Outcomes of Patients With Positive T2Candida Versus Blood Cultures

Outcome	T2Candida Positive (n = 14)	BCx Positive (n = 14)	*P* value
Time to detection of candidemia, h	16.7 (7.5–19)	56 (34–80)	<.0001
Time to antifungal therapy, h	5.6 (−5.8 to 8)[a]	60 (41–84)	<.0001
Source control procedure[b]	7 (50)	11 (79)	.237
Time to source control, h	9 (−2 to 40)	76 (11–106)	.151
Length of hospital stay, d	15.5 (8–29)	16 (10–39)	.659
In-hospital mortality	9 (64)	6 (43)	.450
30-d mortality	10 (71)	6 (43)	.252

Continuous and discrete variables are expressed as median (interquartile range) and No. (%), respectively.

Abbreviation: BCx, blood culture.

[a]Four patients in the T2Candida-positive cohort were started on antifungals prior to T2Candida collection due to the test being requested after operating hours; all 4 received <14 hours of antifungal before invasive candidiasis diagnosis. Time to antifungal treatment was negative in these patients.

[b]Source control was defined as removal of any preexisting central venous catheter or documented surgical or radiologic procedure to drain fluid collections thought to be the source of *Candida* infection.

T2Candida is a US FDA–approved, direct from blood test for candidemia that amplifies *Candida* nucleic acid and detects amplicons with magnetic resonance. It detects **5** major *Candida* species (*C albicans*, *C tropicalis*, *C glabrata*, *C krusei*, & *C parapsilosis*) within 5 hours.

[CRP]/[PCT] in: GNB, GPC, *Candidal* BSI

- [1] 單一革蘭氏**陰性菌**菌血症 (*n* = 362)，[2] 單一革蘭氏**陽性菌**菌血症 (*n* = 132)，和 [3] 單一**念珠菌**黴菌菌血症 (*n* = 36) 引起的敗血症患者，比較三組之間血清 CRP 和 **PCT** 濃度的差異。
- 使用Kolmogorov-Smirnov test，所有組別的這些濃度值，都**不是**常態分佈狀態。
- 上述三組敗血症患者，其中位數 (及 IQR) 的血清 CRP 濃度分別為 15.75 (8.01，24.91)，16.81 (7.04，33.76)，及 11.38 (8.03，21.54) mg/dL。這三組的血漿CRP 濃度差異，以無母數統計 (即: Mann-Whitney U 檢驗) 方法估算，無明顯差異 (所有組別之間差異的 *P* 值，都 >0.05 [i.e., [1] 與 [2] 組，[1] 與 [3] 組，以及 [2] 與 [3] 組之間差異，分別為0.743，0.136，與 0.159])。
- 然而，相同的三組敗血症患者，其**中位數** (及 IQR) 血清 **PCT** 濃度，分別為 20.39 (4.89，77.37)，7.71 (2.82，28.81)，及 3.18 (1.92，11.50) ng/mL，亦使用無母數統計方法估算，就有明顯的差異 (i.e., [1] 與 [2] 組，[1] 與 [3] 組，以及 [2] 與 [3] 組之間差異的 *P* 值，分別為: < 0.001，< 0.001，& 0.019)。所以，在三組敗血症患者之間，使用無母數分析，我們觀察到:

血清 **PCT** 濃度的分佈，比起血清 CRP 濃度的分佈，在三組不同的單一菌血症族群患者之間，差異範圍**更大許多**。

Take Home Message

- 在革蘭氏陰性菌菌血症患者中，尿路感染合併腎臟積水，及糖尿病，會使血漿 **PCT** 濃度傾向於偏**高**的程度; 反之，Pugh-Child C 等級肝硬化，則傾向偏**低**。
- 無論菌血症是由革蘭氏陰性菌，或革蘭氏陽性菌所引起，休克均會使患者的血漿 **PCT** 濃度傾向於較**高**的水平。
- 相較於**慢性**肝臟或腎臟功能障礙患者，急性肝損傷或急性腎損傷患者的基礎血漿 **PCT** 濃度可能較**高**。
- 血漿 **PCT** 濃度，*Candidal* **BSI**: 3~5 ng/mL, & **VRE BSI**: maybe 5~10 ng/mL 。
- 連續監測血漿 **PCT** 濃度 (2-5次)，有助於臨床醫師**早期**發現敗血症治療狀況的**惡化**。

Top Gun 2 Maverick 2022

Thanks for your attention