



核心課程編號：B1

發燒

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學習目標

PGY	UGY
<p><u>知識</u></p> <p>不明熱三大原因之診斷流程 疑似感染患者的處置流程 了解住院病人常見菌血症來源 經驗性抗生素治療 免疫學檢查判讀 腫瘤標記判讀</p> <p><u>技能</u></p> <p>發燒相關的身體檢查</p>	<p><u>知識</u></p> <p>發燒的病理生理機制 影響宿主發燒反應的原因 免疫不全病人族群的不明熱定義 不明熱的定義及意涵 發燒之診斷流程 發燒的初步處置</p> <p><u>技能</u></p> <p>發燒相關的病史詢問</p>



考題

- ❖ 簡述傳統不明熱Fever of unknown origin (FUO)定義？ [10分]
- ❖ 簡述不明熱常見原因 (前3項)？ [10分]
- ❖ 簡述不明熱的診斷流程及處置？ [20分]
- ❖ 列舉三種常見造成不明熱腫瘤？ [10分]
- ❖ 列舉三種常見造成不明熱自體免疫疾病？ [10分]
- ❖ 列舉三種常見造成不明熱感染？ [10分]
- ❖ FUO現在的分類[10分]
- ❖ 列舉Hyperthermia Syndromes常見原因(5項)[20分]



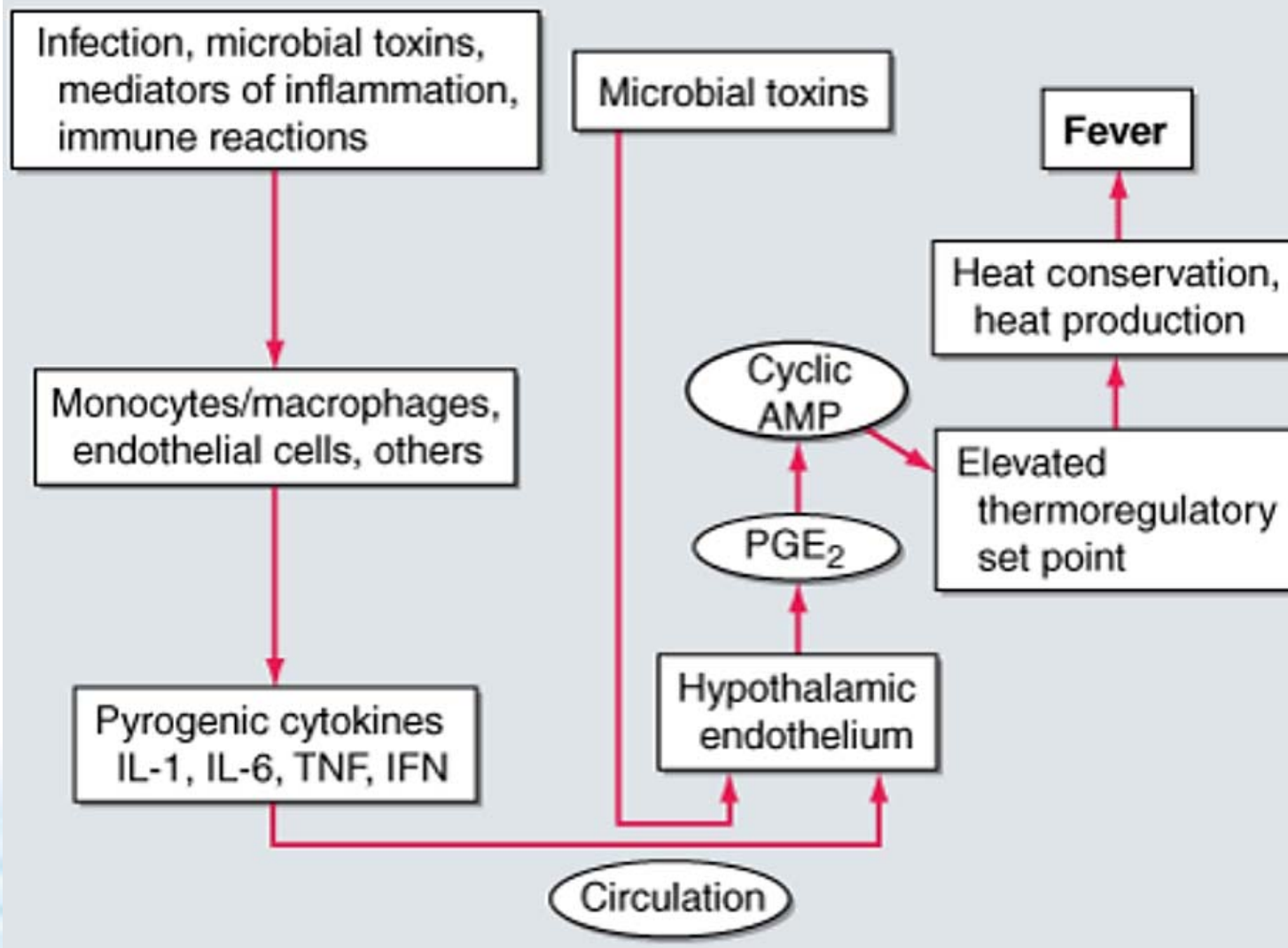
不明熱的定義及意涵

- ❖ Normal : $BT = 36.8^{\circ} \pm 0.4^{\circ} C (98.2^{\circ} \pm 0.7^{\circ} F)$
- ❖ Hypothalamus : controller of BT
- ❖ Daily variation : $0.5^{\circ} C (0.9^{\circ} F)$
- ❖ Fever : $BT \geq 38.3^{\circ} C (101^{\circ} F)$



發燒生理機制

EVENTS REQUIRED FOR FEVER INDUCTION





發燒常見原因

- ❖ Infection
- ❖ Malignancy
- ❖ Systemic inflammatory disease
- ❖ Miscellaneous cause
 - Drug fever
 - Factitious fever
 - Habitual hyperthermia
 - Other (Serotonin syndrome, heat stroke, malignant hyperthermia etc.)



發燒常見原因-1

- ❖ Connective tissue diseases – 22%
- ❖ Infection – 16%
- ❖ Malignancy – 7%
- ❖ Miscellaneous – 4%
- ❖ No diagnosis – 51%



發燒常見原因-2

- ❖ Infection (approximately 25%)
- ❖ Neoplasm
- ❖ Non-infectious inflammatory disease
- ❖ No diagnosis → 50%



發燒相關的病史詢問

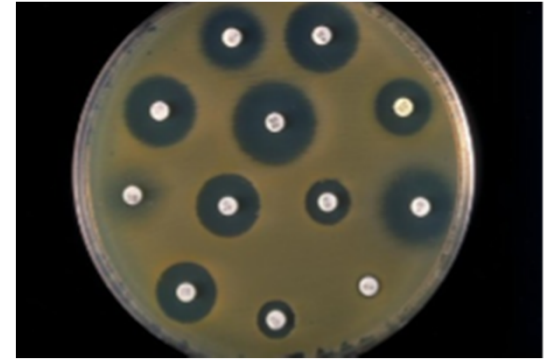
❖ History

- Travel
 - Exposures to toxins, sick persons, animals
 - Immunosuppression
 - Localizing symptoms
 - Look for subtle findings: eg. Jaw claudication, nocturia with prostatitis
- ❖ Degree of fever, nature of fever curve, apparent toxicity, and response to antipyretics not specific enough to guide management



相關的評估檢查

- Clinical diagnosis
 - History, physical exam.
- Laboratory diagnosis
 - culture, serology, etc.
- Image
 - X-ray, CT scan, MRI
 - Sonography
 - PET
 - Nuclear medicine
- Pathology
 - Surgery
 - Biopsy



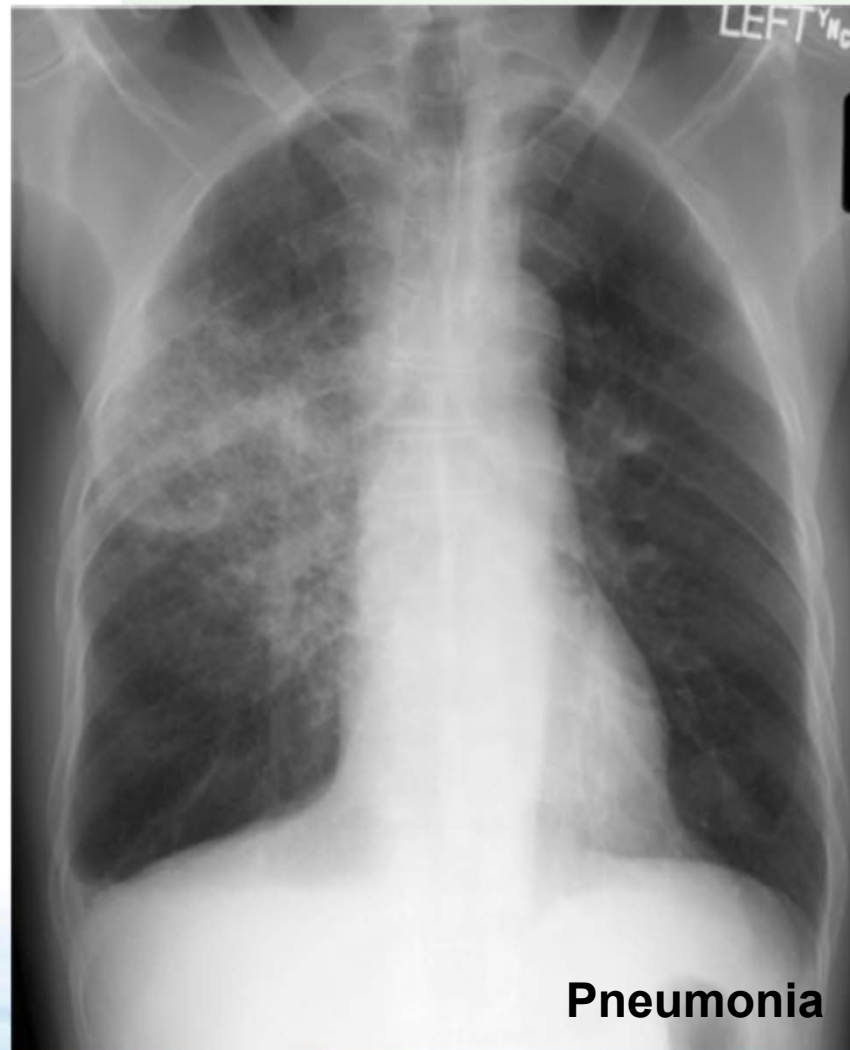


Diagnosis by clinical clue only





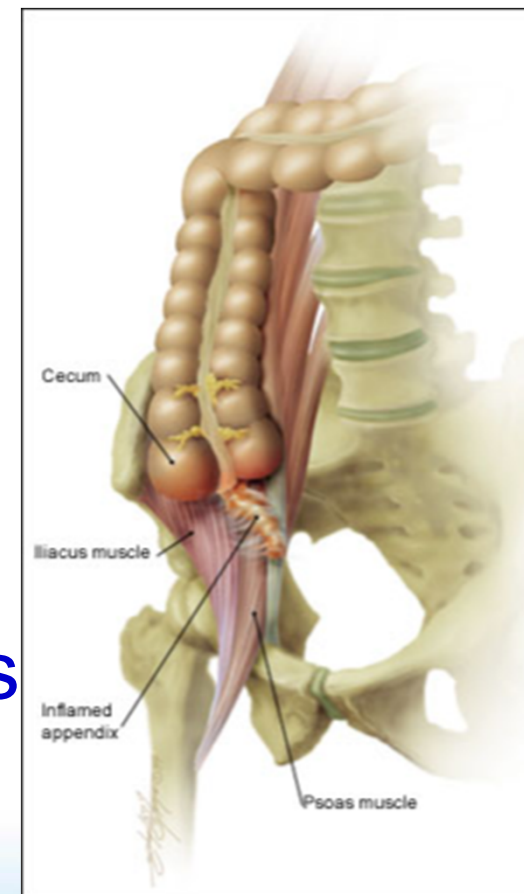
Diagnosis by clinical presentation + Images





Diagnosis by clinical + Lab. or Pathology

- **Clinical + Lab. studies**
 - Acute pyelonephritis
 - Meningitis
 - HIV, AIDS
 - Syphilis
- **Clinical + Pathology**
 - Acute appendicitis
 - Membrane glomerulonephritis
 - Malignancy





發燒的處置流程

- ❖ Repeated examination may be needed
- ❖ Careful attention to skin, mucous membranes, lymph node and abdominal symptoms
- ❖ Yield from history and physical examination unknown



不明熱的診斷流程及處置

Fever > 38°C x 3 weeks; 1 week of "intelligent and invasive investigation"

Physical exam

Repeat history

Laboratory Testing

CBC, Diff, smear, ESR, CRP, urinalysis, liver function tests, muscle enzymes, VDRL, HIV, CMV, EBV, ANA, RF, SPEP, PPD, control skin tests, creatinine, electrolytes, Ca, Fe, transferrin, TIBC, vitamin B₁₂; acute/convalescent serum set aside

Cultures: Blood, urine, sputum, fluids as appropriate

Potentially diagnostic clue^a

No potentially diagnostic clue^a

Directed exam

CT of chest, abdomen, pelvis with IV or PO contrast; colonoscopy

-

+

-

+

⁶⁷Ga scan, ¹¹¹In PMN scan, FDG PET scan

-

+

Needle biopsy^b, invasive testing^c

Diagnosis

No diagnosis

Specific therapy

Empirical therapy^d

Watchful waiting

Anti-TB therapy,
antimicrobial
therapy

Colchicine, NSAIDs

Steroids



Classification of FUO

(Fever of Unknown Origin)

- Classical FUO
- Nosocomial FUO
- Neutropenic FUO
- HIV-associated FUO



Classical FUO

❖ Definition:

- Duration > 3 weeks, evaluation of at least 3 outpatient visits or 3 days in-hospital

❖ Common etiologies:

- Infection, malignancy, CVD



Etiology and Epidemiology of Classical FUO

- ❖ **Infections: Most common cause accounting for 1/3 of cases**
 - TB; Most common infection in non-elderly adults
 - PPD positive in less than 50% of pts with TB and FUO, Sputum samples positive in only 1/4 of patients
 - Abscesses
 - Usually in abdomen or pelvis with some pre-disposing cause (e.g. recent surgery, diabetes, biliary tract disease, recent UTI)
 - Other infections: Osteomyelitis, endocarditis (esp. in pts with recent antibiotic use or HACEK organisms)
- ❖ **Malignancy: Second most common cause**
 - Lymphoma (esp. non-Hodgkin's), Leukemia, Renal cell, HCC, other metastasis to liver
- ❖ **CVD: Third most common cause**
 - Adult Still's disease in younger patients and giant cell arteritis in older patients



Etiology and Epidemiology of Classical FUO - 1

Case studies of fever of unknown origin: prevalent diagnoses

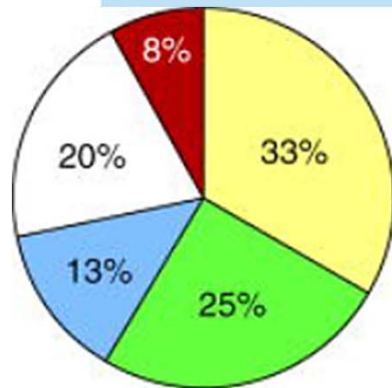
Diagnosis	Case study					
	Alt 1913-30 n = 23	Petersdorf 1952-59 n = 93	de Kleijn 2-94 n = 117	Vanderschueren 1990-99 n = 192	Miller 1989-93 n = 72	Knockaert 1980-89 n = 41
Rheumatic fever	2	6	0	0	0	0
Abdominal abscess	1	4	4	5	0	5
Endocarditis	0	5	4	11	0	2
Syphilis	1	1	1	0	0	0
Mycobacterial	6	12	3	8	57	15
Lymphoma	2	8	11	14	7	5
Solid tumor	3	10	7	7	1	7
Sarcoid	0	2	2	10	0	2
Lupus	0	5	2	8	0	0
Rheumatoid arthritis	0	0	2	20	0	5
Giant cell arteritis	0	2	4	11	0	19
Drug fever	0	1	3	4	0	7
Factitious fever	0	3	2	1	3	0

Numbers represent number of cases.

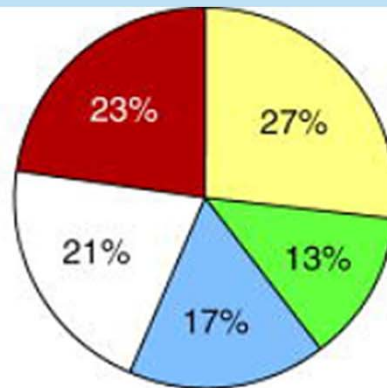
Alt, H, et al. *JAMA* 1930; 94:1457. Petersdorf, RG. *Arch Intern Med* 1992; 152:21. de Kleijn, EM, et al. *Medicine (Baltimore)* 1997; 76:392. Vanderschueren, S, et al. *Arch Intern Med* 2003; 163:1033. Miller, RF, et al. *Int J STD AIDS* 1996; 7:170. Knockaert, DC, et al. *Clin Infect Dis* 1994; 18:601.



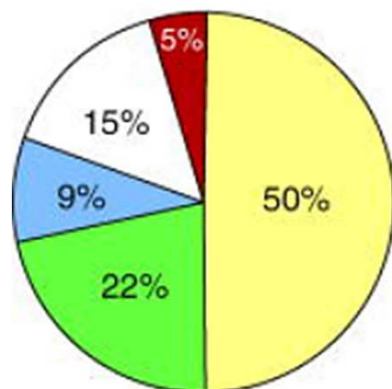
Etiology and Epidemiology of Classical FUO - 2



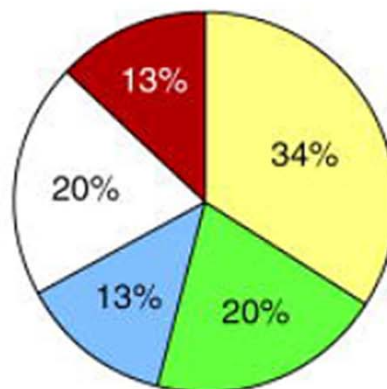
USA



Europe



India



Total



Infections (30–40%)

Tuberculosis
Endocarditis
Localized abscesses (particularly in

Neoplasia (20–30%)

Lymphoma
Renal carcinoma
Gastrointestinal carcinoma
Ovarian carcinoma

Collagen-vascular diseases (15%)

SLE
Rheumatoid arthritis
Vasculitis

Others (15–20%)

Drugs
Pulmonary emboli
Inflammatory bowel disease
Factitious fever
Sarcoidosis



Nosocomial FUO

❖ Definition:

- Hospitalization of at least 24 hrs with no fever on admission, evaluation of at least 3 days

❖ Common etiologies:

- C.Difficile, drugs, pulmonary embolism, septic thrombophlebitis, sinusitis (intubated patients)



Immune-deficient (neutropenic) FUO

(免疫不全病人發燒反應)

❖ Definition:

- Neutrophil count $< 500/\text{mm}^3$, evaluation of at least 3 days

❖ Etiologies:

- Opportunistic bacterial infections, aspergillosis, candidiasis, herpes virus



HIV-Associated FUO

(免疫不全病人發燒反應)

❖ Definition:

- Duration of at least 4 weeks for outpatients and 3 days for inpatients, HIV confirmed

❖ Etiologies:

- Cytomegalovirus, MAI, Pneumocystis, drugs, Kaposi's, lymphoma



Diagnostic Approach – Laboratory Investigations

- ❖ Suggested minimal diagnostic work-up to qualify as FUO has varied over the years
- ❖ Recent article by Mourad et al suggests following as minimal:
 - History and physical examination
 - CBC and differential
 - Blood film reviewed by hematopathologist
 - Routine chemistry including LDH, bilirubin, liver enzymes
 - Urinalysis and microscopy
 - ANA, RH factor
 - HIV
 - CMV IgM; heterophil test if suspicious for Mononucleosis
 - Q-fever serology (if risk exists)
 - CXR
 - Hepatitis serology (if abnormal liver enzymes)



Diagnostic Approach – Investigations and the Evidence

❖ Abdominal CT

- Useful to look for abdominal lymphoma and abscess
- Diagnostic yield in case series 19%
- Clinical follow-up showed that only 1/32 patients with normal scans had an intra-abdominal cause for FUO



Diagnostic Approach – Investigations and the Evidence

❖ Nuclear Imaging:

- For localizing inflammatory or infectious focus
- Technetium scans likely have best test characteristics overall and should be test of choice
 - Technetium studies: specificity 93%, sensitivity 40-75%
 - Indium-labeled WBC scans: specificity 69%-86%, sensitivity 45%-82%
 - Gallium scans: (limited studies)



Diagnostic Approach – Investigations and the Evidence

❖ Duke criteria for endocarditis:

- Endocardities: 1-5% of all cases of FUO
- Sensitivity 82%, specificity 99%

❖ Liver Biopsy:

- Diagnostic yield 14%-17% regardless of whether abnormal physical exam or liver enzymes exist
- Complications in FUO from biopsy only 0.32% at most
- Recommended



Diagnostic Approach – Investigations and the Evidence

- ❖ **Temporal artery biopsy**
 - Large studies comprised of elderly with FUO lacking
 - Arteritis cause of FUO ~16% of pts (All comers)
 - Safe, recommended in elderly with FUO

- ❖ **Leg dopplers**
 - DVT cause of FUO ~ 2-6% of pts
 - Safe, easy to do, recommended



Diagnostic Approach – Investigations and the Evidence

❖ Bone Marrow Examination

- Diagnostic yield of culture 0-2%
- Not recommended in immunocompetent pts

❖ Abdominal exploration

- Role of surgery in post-CT era uncertain

❖ Empiric Therapy (antibiotics, anti-TB, steroids)

- Not studied
- Not recommended



常見腫瘤標記判讀

Tumor marker	Associated tumor types
<u>Alpha fetoprotein (AFP)</u>	<u>germ cell tumor, hepatocellular carcinoma</u> ^[5]
<u>CA15-3</u>	<u>breast cancer</u> ^[6]
<u>CA27-29</u>	<u>breast cancer</u>
<u>CA19-9</u>	Mainly <u>pancreatic cancer</u> , but also <u>colorectal cancer</u> and other types of <u>gastrointestinal cancer</u> . ^[7]
<u>CA-125</u>	Mainly <u>ovarian cancer</u> , ^[8] but may also be elevated in for example <u>endometrial cancer, fallopian tube cancer, lung cancer, breast cancer</u> and <u>gastrointestinal cancer</u> . ^[9] May also increase in <u>endometriosis</u> . ^[10]
<u>Calretinin</u>	<u>mesothelioma, sex cord-gonadal stromal tumour, adrenocortical carcinoma, synovial sarcoma</u> ^[5]
<u>Carcinoembryonic antigen</u>	<u>gastrointestinal cancer, cervix cancer, lung cancer, ovarian cancer, breast cancer, urinary tract cancer</u> ^[5]
<u>CD34</u>	<u>hemangiopericytoma/solitary fibrous tumor, pleomorphic lipoma, gastrointestinal stromal tumor, dermatofibrosarcoma protuberans</u> ^[5]
<u>CD99</u>	<u>Ewing sarcoma, primitive neuroectodermal tumor, hemangiopericytoma/solitary fibrous tumor, synovial sarcoma, lymphoma, leukemia, sex cord-gonadal stromal tumour</u> ^[5]



血清免疫學檢查

檢驗項目	中文名稱	檢體	參考值	單位
AchRAb (Acetylcholine receptor antibody)	醃膽素受器抗體	血清	<0.2	nmol/L
Rheumatoid factor— Latex	類風濕性關節炎因子檢查— 乳膠凝集法定性	血液	沒反應(陰性)	
Rheumatoid factor test—Nephelometry	類風濕性關節炎因子—定量	血液	0-14	IU/ml
Mycoplasma pneumonia Ab	肺炎黴漿菌抗體試驗	血液	>1:40X有意義	
Widal & Weil-Felix test	發熱疾病的凝集試驗	血液		
ANA (antinuclear antibody)	抗細胞核抗體 FIA法	血液	見備註	FA titer
Cold hemoagglutinin	寒冷凝集反應	血液	>1:32X有意義	
Amebiasis Ab test(IHA)	人體阿米巴體之偵測測驗	血液	>1:16X有意義	
C'3—Nephelometry	血液補體—3 測定 (包括C3c)	血液	90-180	mg/dl
C'4—Nephelometry	血液補體—4 測定	血液	10-40	mg/dl
HLA-B27 Tissue typing	組織抗原配合試驗 HLA—27	血液	(-) 陰性反應	
ASLO, anti-streptolysin-O test	抗鏈球菌溶血素O 效價測定	血液	<200	
Anti-DNA (FIA)	DNA抗體	血液	<10X(-)	FA titer
Legionnaires' disease test	退伍軍人症血清檢查	血液	1:100(-)	



住院病人菌血症來源

表二 1993-2000 年成人加護病房院內菌血症之感染來源與致病菌之分布情形

感染來源	感染人次 (%)	死亡數 (%)	GPC	Enterobacteriaceae	GNF-GNB	Anaerobes	Fungi	Polymicrobial
原因不明	356(52.0)	131(36.8)	86	72	119	6	31	42
下呼吸道	112(16.4)	41(36.6)	23	19	52	0	1	17
血管內導管裝置	56(8.2)	19(33.9)	15	9	15	0	5	12
泌尿道	36(5.3)	16(44.4)	3	9	6	0	12	6
外科部位	10(1.5)	3(30.0)	3	2	3	0	0	2
腸胃道	3(0.4)	3(100.0)	0	1	1	0	1	0
皮膚與軟組織	2(0.3)	0 (0.0)	1	0	0	0	1	0
其它部位	1(0.1)	0 (0.0)	0	0	0	0	0	1
多重部位	109(15.9)	45(41.3)	35	18	13	0	16	27
合計	685(100.0)	258(37.7)	166	130	209	6	67	107

GPC：革蘭氏陽性球菌

GNFGNB：葡萄糖非發酵性革蘭氏陰性桿菌

fungi：黴菌

多重部位：≥ 2 個部位之感染來源

Enterobacteriaceae：腸內菌屬

Anaerobes：厭氧菌

其它部位：會陰部位之分泌物



經驗性抗生素治療

- ❖ 一般不明熱病人不建議使用經驗性抗生素治療查出原因才是重點
- ❖ 對於免疫低下或中性球缺少個案，因個案可能因免疫低下而症狀不明顯，則建議給予第四代頭芽孢素治療