Superbugs
Tigelin Clinical Use

New Class
of Broad-Spectrum Antibiotics

Yih-Ming, Su

地區醫院的危機?

1. 安寧治療，不插管，使地區醫院呼吸器依賴的病人來源減少，佔床率下降。
2. 轉入RCW的病人大都經歷醫學中心，區域教學醫院ICU，RCC治療無法脫離呼吸器及狀況差的病人才會下轉RCW。這些病人身上都常有各種抗藥性的細菌移生。由於易發生感染因而須要後線抗生素，造成醫院的藥費成本增加。
3. 病人來源減少，醫院之間相互競爭的結果，每個病人每月須自費看護費由25,000元降至5000元甚至不收費用。
4. 水電費，藥品費，及其他之消耗品的漲價。人事費(一例一休)

由於上述之因素造成醫院成本增加。經營愈困難。

據健保署統計
住診醫療費用占比率

各級醫院	95年度	109年度
醫學中心	31.8%	34.5%
區域醫院	27.0%	33.0%
地區醫院	16.6%	11.8%
基層診所	24.6%	20.7%

可見區域級醫院持續成長上升，地區醫院與基層逐漸式微，顯示臺灣醫療體系嚴重失衡。

台灣醫療院所層級分佈

	醫學中心	區域醫院	地區醫院
2000	18	64	447
2001	18	63	405
2002	18	70	407
2003	18	71	397
2004	19	71	366
張上淳, 院內感染雜誌 2006, 8			
2014 (3月)	22	83	366
衛生福利部中央健康保險署			

住院病人抗生素使用情形

	總住院			加護病房	
	人數	抗生素處方率(%)	抗生素藥費比率(%)	抗生素處方率(%)	抗生素藥費比率(%)
2000	21,401	64.6	43.1	80.7	65.4
2001	21,654	63.8	43.7	79.6	63.4
2002	21,869	63.1	45.1	79.6	61.6
2003	21,984	63.4	45.2	80.3	59.5
2004	22,134	62.0	44.4	80.4	59.6

張上淳, 院內感染雜誌 2006, 8

Struggle Against Infectious Diseases"

"History of humankind can be regarded from a medicinal point of view as a struggle against infectious diseases"

Yoneyama, H., Katsumata, R., *Biosci. Biotechnol. Biochem.*, 2006, *70*,1060

人類和細菌是一場永不停止的戰爭

dodd.cmcvellore.ac.in, www.ayurvedicmedicine4u.com, www.rootsweb.com

上帝創造萬物包括細菌?

人類發現及製造抗生素可以殺菌，由於不當的使用在抗生素的選擇壓力產生超級細菌

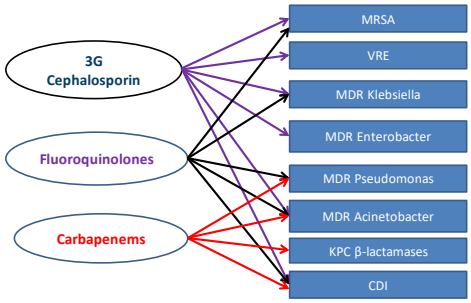
院內感控沒有作好使得超級細菌得於院內散播？

為何出現超級細菌

- 某一些細菌，天生即存在可以對某一類或某些類抗生素產生抗藥性基因。
- 在演化的過程中，累積突變產生抗變性。
- 無抗藥性的細菌從有抗藥性的細菌中，得到有抗藥性的基因。

超級細菌的產生

Antibiotic Coverage-Collateral Damage



Troublesome Bacteria Redefining ESKAPE as ESCAPE

E *Enterococcus faecium*

S *Staphylococcus aureus*

C *Clostridium difficile* → Acknowledges the growing virulence of *C. difficile*

A *Acinetobacter baumannii*

P *Pseudomonas aeruginosa*

E *Enterobacteriaceae* → Captures *Klebsiella*, *Enterobacter*, and other resistant species including *E. coli* and *Proteus sp.*

K. pneumonia

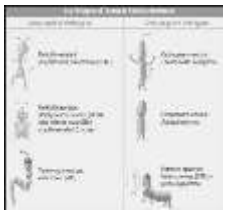
Enterobacter species

〝ESCAPE〞 Pathogens

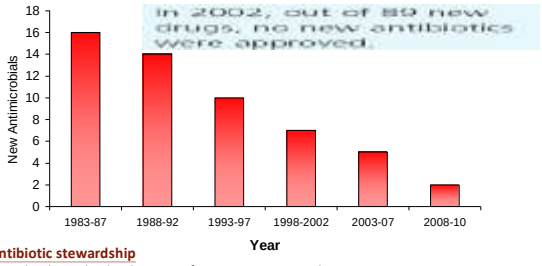
◈Bad bugs, no drugs：

〝**Escape**〞 from the effects of antibacterial agents or the non-existence of newer active antibiotics

Boucher HW, Talbot GH, Bradley JS, et al Clin Infection Dis 2009;48:1-12



… As Antibiotic Options Decline Rapidly



Antibiotic stewardship

There has been the development of some new agents with activity against resistant gram positive organisms such as linezolid, tigecycline, daptomycin, telavancin, ceftobiprole, and ceftaroline. However, there is no new agents on the immediate horizon for the treatment of resistant gram-negative organisms. There are some agents in pre-clinical studies, but it will be 10-15 years before any of them may be available for clinical use.

Factors for Acquisition of MDROs

(CID2006; 43:S57–61)

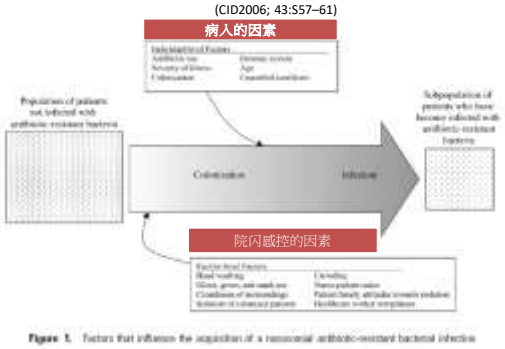
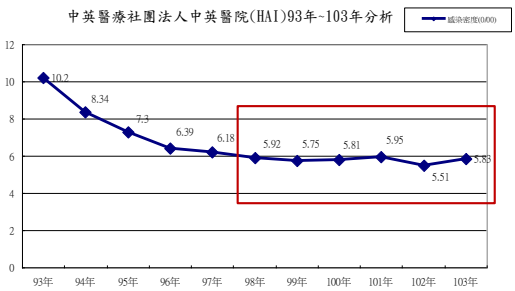
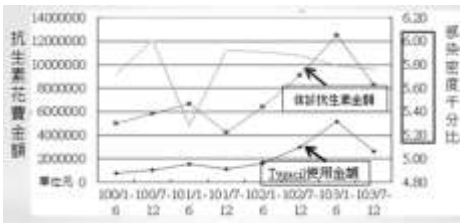
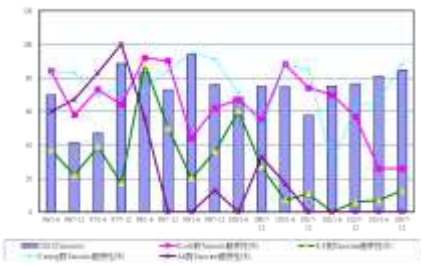


Figure 1. Factors that influence the acquisition of a nosocomial antibiotic-resistant bacterial infection







Defined Daily Dose (DDD)

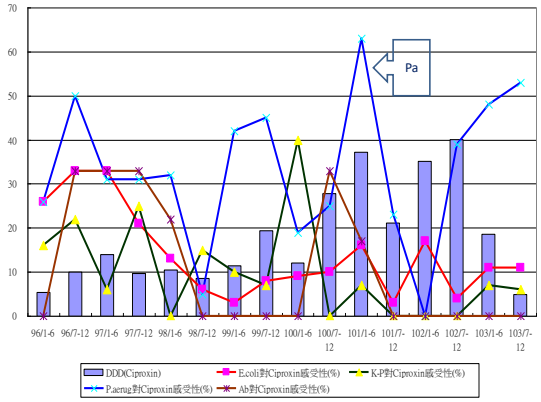
DDD = 藥物使用量/入院人日數/ 網查開不同藥物的數值

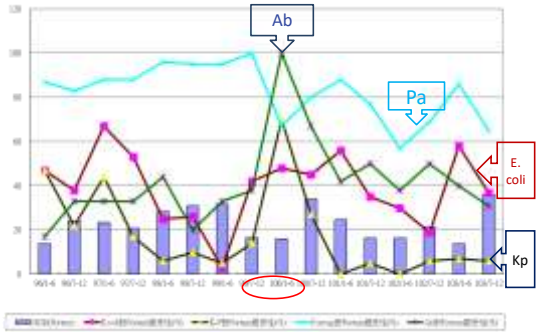
如Tazocin：38184750/32925/14=82.84

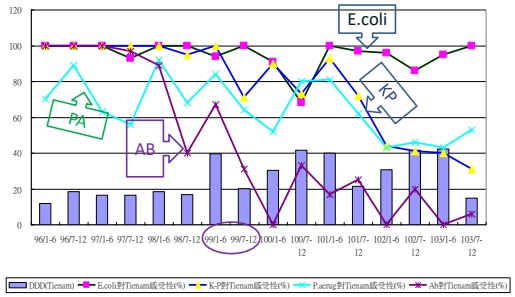
Tienam：1890500/32925/2=28.71

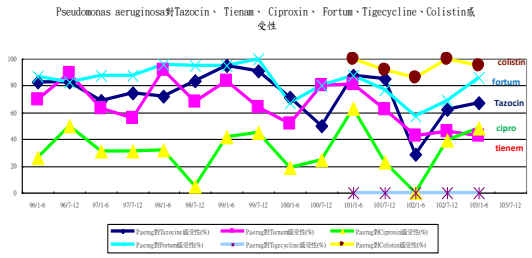
查閱方式

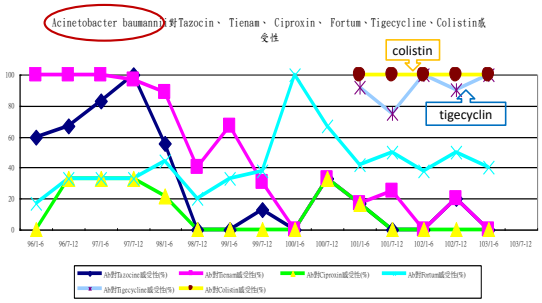

1
2
3
4


Pa
DDD(Ciproxin)
E.coli對Ciproxin感受性(%)
K-P對Ciproxin感受性(%)
P.aerug對Ciproxin感受性(%)
Ab對Ciproxin感受性(%)

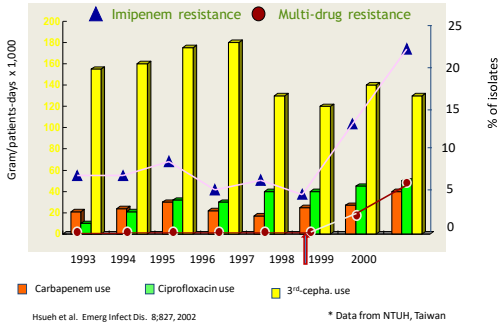

Ab
Pa
E. coli
Kp

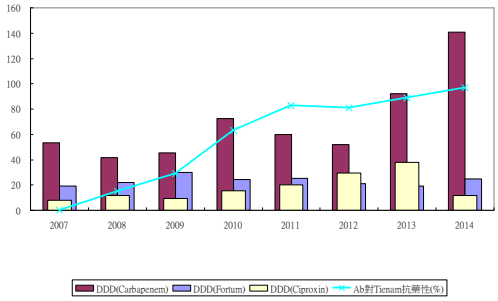

E.coli
PA
AB
KP
DDD(Tienam)
E.coli對Tienam感受性(%)
K-P對Tienam感受性(%)
P.aerug對Tienam感受性(%)
Ab對Tienam感受性(%)


Pseudomonas aeruginosa對Tazocin、 Tienam、 Ciproxin、 Fortum、Tigecycline、Colistin感受性
colistin
fortum
Tazocin
cipro
tienem

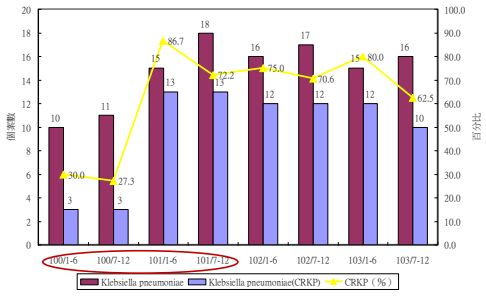

Acinetobacter baumanni對Tazocin、 Tienam、 Ciproxin、 Fortum、Tigecycline、Colistin感受性
colistin
tigecyclin

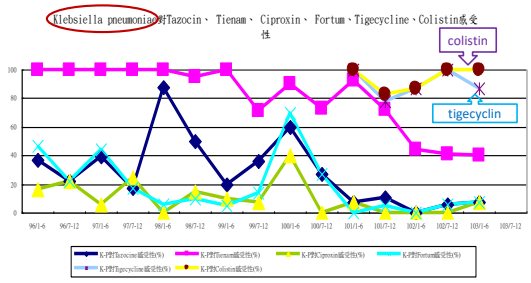
Emergence of MDR *Acinetobacter* in Taiwan





中英醫院院內感染CRKP趨勢圖





Antimicrobial Stewardship

A rational, systematic approach to the use of antimicrobial agents in order to achieve optimal patient outcomes

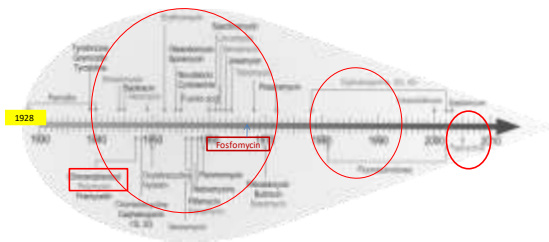
- Reducing colonization and infection
- Reducing volume of antimicrobial use
- When decision made to treat Cure/prevent Infection
  - Use right drug
  - Right dose
  - Right duration

  → Minimize Toxicity, Decrease Resistance

Treat infection, not contamination, no colonization.

Use local data

新的Antibiotics研發越來越少

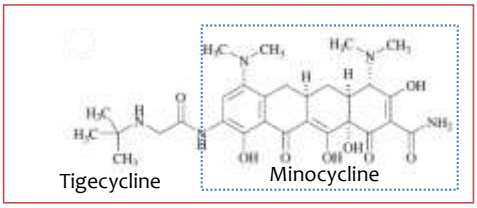


Tigelin

虎霸 Lyo. Injection 50mg

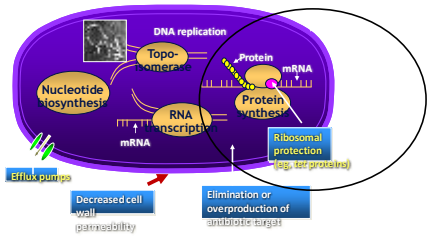
Tigelin Introduction

- 藥理分類：Glycylcline
- Tigelin為minocycline的衍生物
  - 增強抗菌範圍：G(+),G(-),anaerobes
  - 迴避抗藥性機制



Tigelin作用機轉

- tigelin是藉由細菌內單30S ribosome的部位結合來破壞細菌細胞內的反應因此阻止蛋白質的合成. tigelin 與30S ribosome的A位置結合的方法是與tetracycline不同的. tigelin是與30S ribosome的附加部位作結合.這種種的結合方式與能力.使tigelin可以克服tetracycline抗藥的機轉.可以作用在具抗藥性的菌種上.



What is Tigelin?

- 藥理分類：Glycylcline
- 產品名：Tigelin® Lyo. for Inj. 50mg
  虎霸®凍晶注射劑50毫克
- 原廠名： Tigecycline (Tygacil ®) 老虎黴素 (輝瑞)
- 適應症：對Tigelin具有感受性之細菌所引起之複雜性皮膚及皮膚結構感染(cSSSI)、複雜性腹腔內感染症(cIAI)及社區感染性肺炎(CAP)。
  嚴重感染症
- 用法用量：100mg loading, then 50mg q12h
  –腎功能不全患者不需調整劑量
- 副作用：噁心、嘔吐

In Vitro Activity of Tygacil* Against Common Pathogens

Gram-positive Bacteria
- *S. aureus*
- *E. faecium*
- *E. faecalis*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group
- *Streptococcus pyogenes*

Anaerobes
- *B. fragilis* group
- *Prevotella* spp.
- *Peptostreptococcus* spp.
- *C. perfringens*

Others
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*
- *Rapid Growing Mycobacteria (RGM)*

Gram-negative Bacteria
- *E. coli*
- *Klebsiella* spp.
- *Acinetobacter baumannii*
- *Citrobacter freundii*
- *Enterobacter cloacae*
- *Enterobacter aerogenes*
- *Stenotrophomonas maltophilia*

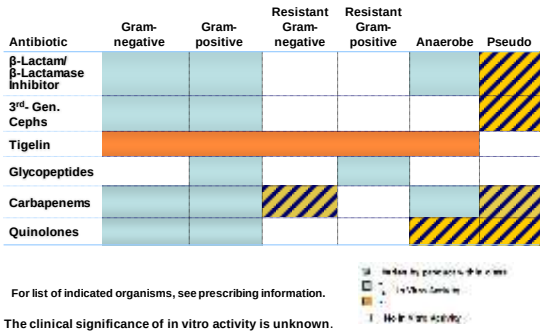
Not Pseudomonas and Proteus

The clinical significance of in vitro activity is unknown.
Tygacil® (tigecycline) Prescribing Information.
*trademark

經驗抗生素選擇：
Pip-taz 、carbapenem 、tigelin抗菌範的比較

			Tigelin
OSSA	+	+	+
ORSA	-	-	+
Ampicillin-sensitive enterococci	+	+	+
Ampicillin-resistant enterococci	-	-	+
Enterobacteriecae	+	+	+
★ *Pseudomonas aeruginosa*	+	+	-
Acinetpbacter baumanii	-	+	+
CRAB	-	-	+
產生ESBL綱菌	-	+	+
產生ESBL綱菌	-	+	+
Anaerobes	+	+	+

Tigelin: An Expanded Broad Spectrum of In Vitro Activity



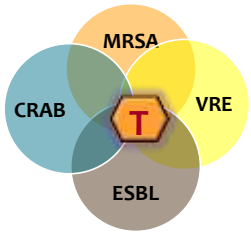
For list of indicated organisms, see prescribing information.

The clinical significance of in vitro activity is unknown.

Tigelin的臨床使用

- 致病菌包括抗藥性GPC的混合感染 (最重要够臨床適應症：
  1. Postlaparatomy wound infections
  2. Intraabdominal infection
  3. Diabetic foot infection
  4. Pressure sores
  5. Deep neck infections
  6. Hospital-acquired pneumonia
  7. Necrotizing fascitis (ORSA 、 Vibrio 、Aeromonas)
  8. Postoperation wound infection
- 抗藥性GNB感染症：
  1. Carbapenem resistant A. baumonnii (CDAB)感染症
  2. 〝產生ESBL細菌〞感染症
  3. 〝產生AmpC β-lactamase細菌〞感染症

Tigelin®特點



- 單一藥物就能對抗多種抗藥性細菌。
- 治療多種抗藥性的細菌感染症 (?)：tigelin可以“一槍打數鳥”

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In-vitro Activity against A. baumannii

A. baumannii (n=851)	MIC (μg/mL)		
	MIC_{50}	MIC_{90}	Range
Tigelin	0.5	1	0.03-8
Pip/taz	8	≥ 256	≤ 0.06- ≥ 256
Ceftazidime	16	≥ 64	≤ 8- ≥ 64
Cefepime	16	≥ 64	≤ 0.5- ≥ 64
Imipenem	0.5	16	≤ 0.06- ≥ 32
Levofloxacin	4	≥ 16	0.015- ≥ 16
Amikacin	4	32	≤ 0.5- ≥ 128

Waltes KB. Antimicrob Agents Chemother 2006;50:3479-84.

Treatment of multidrugresistant (MDR) Gram-negative pathogens

Antibiotic regimens for treatment of infections due to multidrug-resistant Gram-negative pathogens: An evidence based literature review

Mandana Izadpanah J Res Pharm Pract. 2015 JulSep; 4(3): 105–114

Abstract

Evidences regarding the efficacy of different antibiotic regimens proposed for treatment of **multidrug-resistant (MDR) Gram-negative pathogens** have been reviewed. **Available data in Scopus, Medline, EMBASE, the Cochrane central register of controlled trials, and Cochrane database of systematic reviews have been collected.** Several antibiotic regimens are proposed for treatment of MDR Gram-negative infections (defined as nonsusceptibility to at least one agent in three or more antimicrobial categories). The most challenging issue is the treatment of **carbapenem-resistant (CR) Gram-negative pathogens. A carbapenem plus either colistin or tigecycline was the most effective regimen for treatment of CR Gram-negative pathogens with low level resistance (minimal inhibitory concentration [MIC] ≤ 8 mg/L). However, in high level resistance (MIC > 8 mg/L), combination of colistin and tigecycline showed promising effect.**

Definitions

- **MDR (multidrug-resistant)**
  - Resistant to ≥3 classes of antimicrobial agents
- **XDR (extensively drug-resistant)**
  - Resistant to all but 1 or 2 (colistin or tigecycline)
- **PDR (pandrug-resistant)**
  - Resistant to all*

*Antimicrobial agents that are available at the time of use of the definition and in most parts of the world and that are regarded as potentially effective against the respective pathogens

Falagas ME et al. *Clin Infect Dis* 2008;41:848-54.

Antimicrobial Stewardship

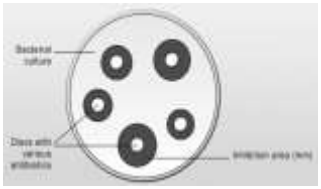
A rational, systematic approach to the use of antimicrobial agents in order to achieve optimal patient outcomes

- **Reducing colonization and infection**
- **Reducing volume of antimicrobial use**
- **When decision made to treat:**
  - **Use right drug**
  - **Right dose**
  - **Right duration**

  → **Cure/prevent Infection**
  Minimize Toxicity
  Decrease Resistance

Treat infection, not contamination, no colonization.
Use local data

Disk Diffusion Method 瓊脂擴散試驗



瓊脂擴散試驗也稱作“紙錠試驗（disc test）”：測試某培養菌株對不同抗感染藥物的抗藥性。依據抑菌環，可以區分為“敏感性”、“抗藥性”或“介於兩者中間”。此界定值是以不同的藥動力學參數為基礎而建立的標準劑量，考量要點包了藥物血中濃度、組織中濃度、半衰期、AUC、及臨床試驗結果。

下列狀況單獨使用Tigecycline作為經驗性抗生素時會治療失敗

- 組織的抗生素濃度太低：
  1. Bacteremia (嚴重感染症可能會併發**bacteremia**，tigecycline的血清濃度太低)
  2. Urinary tract infection (大部分的tigecycline由肝臟排泄，尿液濃度大約只有血清濃度的25%)
  3. CNS infections (tigecycline不能穿透BBB)
- 對下列 G(-) bacilli缺乏抗菌效力：
  a. Pseudomonas aeruginosa
  b. Proteus sp (Proteus mirabilis 、 Proteus valgaris)
  c. Providencia spp
  d. Morganella morganii
  e. Burkholderia cepacia
- Bacteriostatic

時間依賴型抗生素

- 臨床效果與藥物濃度超過細菌MIC值的時間所佔投藥間隔的比率(%T > MIC)有很大的關係。
- 以Doripenem為例當%T > MIC的百分比達到40%時，藥物就會有殺菌作用，而百分比若是在20%時，則只能達到抑菌的效果。

	% Time > MIC	
	Static (%)	Bactericidal* (%)
Cephalosporins	35 - 40	60 - 70
Penicillins	30	50
Carbapenems	20	40

MIC = minimum inhibitory concentration
*3 log reduction in colony-forming units.

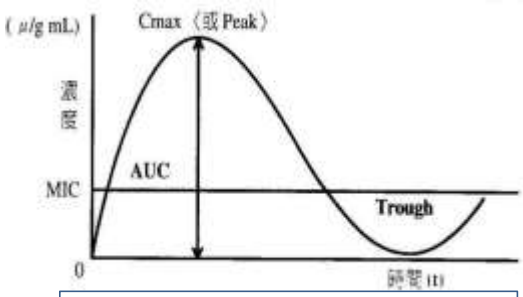
1. Drusano GL. *Nat Rev Microbiol.* 2004;2:289-300.

PK參數、PD參數名詞解釋

評估藥物的藥理作用及效果的兩種參數：

- 體內動態參數（藥物動力學：pharmacokinetics，PK）
- 表示藥效強度的參數（藥效學：pharmacodynamics，PD）

抗生素治療時，利用這些參數組合來進行抗生素的給與計劃、療效預測以及防止抗藥性菌株產生之給藥模式的參考。



所給與的藥品依體內代謝不同的時間點，畫出了血中濃度變化曲線
Cmax（或是Peak值）：曲線頂點最高血中濃度濃度。
Trough值：Cmax之後，藥物濃度會逐漸減少，而且在下一次投藥前，藥物濃度達最低點。
AUC :藥物血中濃度變化曲線下方的面積

PD（Pharmacodynamics：藥效學）

- 藥物的作用活性－即量化之抗感染藥物效應。Penicillin G，一直是具有最廣效用活性的抗生素，Penicillin作用在敏感的細菌上（鏈條菌、奈氏雙球菌）只需要0.01 mg/L的濃度，而其它的抗傳染製劑則需要100倍以上的濃度，有時候甚至1000倍（1~10 mg/L）。
- 藥物的作用品質（同義：作用型態），有兩種不同的形式：
  * 抑菌作用（bacteriostasis）：可逆性地抑制生長，抗傳染藥物無法完 全將組織中的致病菌消滅，個體的“治癒”需要抗傳染藥物以及宿主體內特異性與非特異性的防禦機制共同作用。
  * 殺菌作用（bacteriocide）：不可逆性地抑制生長。

PD（Pharmacodynamics：藥效學）

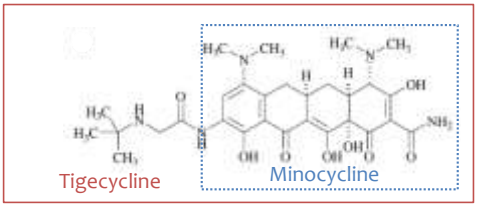
- 個體感染的“治癒”需要抗傳染藥物以及宿主體內特異性與非特異性的防禦機制共同作用；
- 防禦機制作用很弱的地方（心內膜），中央有化膿性傷口，且體內不具有功能性吞噬細胞，或是免疫系統不健全，此類情況下則**必需**使用殺菌藥物。
- 在個體完全不具有防禦機制的情況下，使用殺菌藥物也有可能無法將 全部的細菌除去，因為在細菌族群中都會存有一些細胞，具有抵抗藥物的表現型，但其基因型卻不具有抗藥物基因，這些細菌稱作**持續菌（persister）**，在藥劑培養中可以觀察到發生率為1：10^6到1：10^8

Pneumonia/ventilator associated Pneumonia

Ventilato rassociated Pneumonia and tracheobronchitis followed by
bacteremia are the most frequent common infectious complications in critically ill patients. Late onset VAP, which occurs after 4 days of intubation, mainly is induced by MDR bacteria such as MRSA, Ab, Pa, Kp and ESBL gbacteria.[40] In the empirical treatment of VAP due to the MDR pathogens, local resistance patterns are determining factor. In most cases, CMS and tigecycline are the unique treatment options for VAP caused by MDR
pathogens.[41,42,43,44,45]

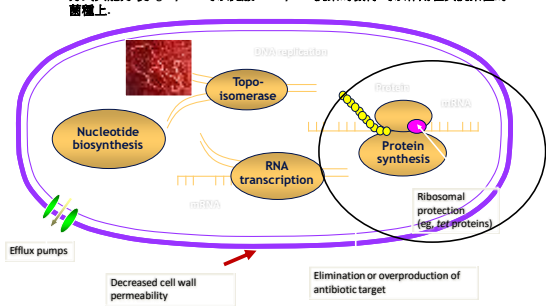
Tigelin Introduction

- 藥理分類：Glycylcline
- Tigecycline為minocycline的衍生物
  - 增強抗菌範圍：G(+),G(-),anaerobes
  - 迴避抗藥性機制



Tigelin作用機轉

- **tigecycline是藉由細菌內單30S ribosome的部位結合來破壞細菌細胞內的反應因此阻止蛋白質的合成. tigecycline 與30S ribosome的A位置結合的方法是與tetracycline不同的. tigecycline是與30S ribosome的附加部位作結合.這種種的結合方式與能力.使tigecycline可以克服tetracycline抗藥的機轉.可以作用在具抗藥性的菌種上.**



What is Tigecycline?

- 藥理分類：Glycylcline
- 產品名：Tigelin® Lyo. for Inj. 50mg
  虎霸®凍晶注射劑50毫克
- 原廠名：Tygacil ® 老虎黴素 (輝瑞)

- 適應症：對Tigecycline具有感受性之細菌所引起之複雜性皮膚及皮膚結構感染(cSSSI)、複雜性腹腔內感染症(cIAI)及社區感染性肺炎(CAP)。

嚴重感染症

- 用法用量：100mg loading, then 50mg q12h
  –腎功能不全患者不需調整劑量
- 副作用：噁心、嘔吐

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In Vitro Activity of Tygacil* Against Common Pathogens

Gram-positive Bacteria
- *S. aureus*
- *E. faecium*
- *E. faecalis*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group
- *Streptococcus pyogenes*

Anaerobes
- *B. fragilis* group
- *Prevotella* spp.
- *Peptostreptococcus* spp.
- *C. perfringens*

Others
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*
- *Rapid Growing Mycobacteria (RGM)*

Gram-negative Bacteria
- *E. coli*
- *Klebsiella* spp.
- *Acinetobacter baumannii*
- *Citrobacter freundii*
- *Enterobacter cloacae*
- *Enterobacter aerogenes*
- *Stenotrophomonas maltophilia*

Not Pseudomonas and Proteus

The clinical significance of in vitro activity is unknown.
Tygacil® (tigecycline) Prescribing Information.
***trademark**

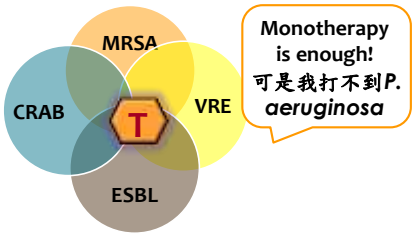
經驗抗生素選擇：
Pip-taz 、carbapenem 、tigelin抗菌範的比較

			Tigelin
OSSA	+	+	+
ORSA	-	-	+
Ampicillin-sensitive enterococci	+	+	+
Ampicillin-resistant enterococci	-	-	+
Enterobacteriecae	+	+	+
Pseudomonas aeruginosa	**+**	**+**	**-**
Acinetpbacter baumanii	-	+	+
CRAB	-	-	+
產生ESBL鋼菌	-	+	+
產生ESBL鋼菌	-	+	+
Anaerobes	+	+	+

Tigecyclin的臨床使用

- 致病菌包括抗藥性GPC的混合感染 (最重要够臨床適應症：
  1. Postlaparatomy wound infections
  2. Intraabdominal infection
  3. Diabetic foot infection
  4. Pressure sores
  5. Deep neck infections
  6. Hospital-acquired pneumonia
  7. Necrotizing fascitis (ORSA 、 Vibrio 、Aeromonas)
  8. Postoperation wound infection
- 抗藥性GNB感染症：
  1. Carbapenem resistant A. baumonnii (CDAB)感染症
  2. 〝產生ESBL細菌〞感染症
  3. 〝產生AmpC β-lactamase細菌〞感染症

Tigelin®特點



- 單一藥物就能對抗多種抗藥性細菌。
- 治療多種抗藥性的細菌感染症 (?)：tigecycline可以“一槍打數鳥”

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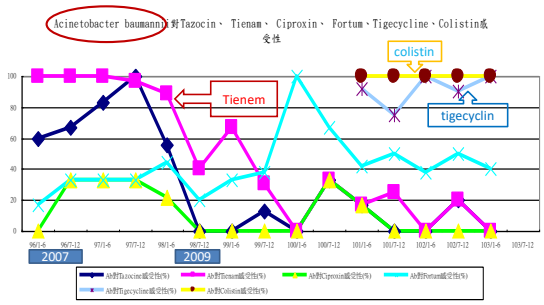
In-vitro Activity against A. baumannii

A. baumannii (n=851)	MIC (μg/mL)		
	MIC_{50}	MIC_{90}	Range
Tigecycline	0.5	1	0.03-8
Pip/taz	8	≥ 256	≤ 0.06- ≥ 256
Ceftazidime	16	≥ 64	≤ 8- ≥ 64
Cefepime	16	≥ 64	≤ 0.5- ≥ 64
Imipenem	0.5	16	≤ 0.06- ≥ 32
Levofloxacin	4	≥ 16	0.015- ≥ 16
Amikacin	4	32	≤ 0.5- ≥ 128

Waltes KB. Antimicrob Agents Chemother 2006;50:3479-84.



Tigecycline
v.s.
ESBL-E. coli

Bacteria	MIC (μg/mL)		
	Range	MIC_{50}	MIC_{90}
ESBL	**0.047-0.75**	**0.125**	**0.38**
CTX-M-9	0.047-0.75	0.125	0.38
SHV	0.064-0.75	0.19	0.5

Tigecycline MIC breakpoints (FDA):
Enterobactereaceae: 2 μg/mL, Non-fermentative GNB: 2 μg/mL

Sorlozano A. Int J Antimicrob Agents 2006;28:532-6.

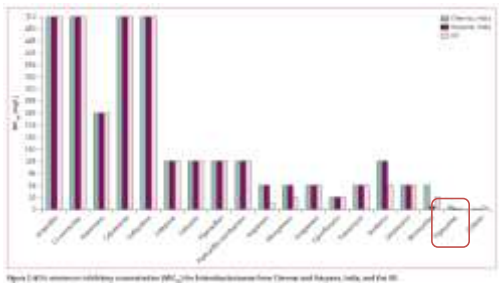
In-vitro Activities
(% susceptible) against
MRSA and VRE

Antibiotics	MRSA (n=348)	E. faecium VRE (n=77)	E. faecalis VRE (n=11)
Tigecycline	98.9	100	100
Levofloxacin	17	0	9.1
Linezolid	100	99.1	100
Minocycline	96.8	62.3	36.4
Vancomycin	99.7	-	-

Breakpoint of tigecycline: ≤0.5 μg/mL for Staphylococcus, ≤0.25 mg/mL for Enterococcus

Hoban DJ. Diagn Microbiol Infect Dis 2005;25:215-27.

MIC for NDM-1from
India & UK



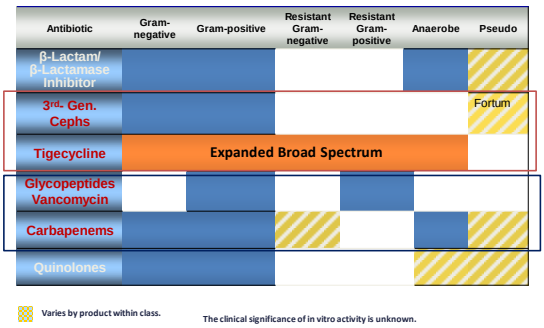
Tigelin組織濃度

- **組織濃度高：**
  - 膽囊gallbladder
  - 結腸colon
  - 皮膚水泡液skin blister fluid
  - 肺泡細胞alveolar cells
  - 肺部lung
  - 肺部上皮內襯液lung epithelial lining fluid;ELF
- **組織濃度低：**
  - 骨頭bone
  - 關節滑液synovial fluid

下列狀況單獨使用Tigecycline作為經驗性抗生素時會治療失敗

- **組織的抗生素濃度太低：**
  1. Bacteremia (嚴重感染症可能會併發**bacteremia**，tigecycline的血清濃度太低)
  2. Urinary tract infection (大部分的tigecycline由肝臟排泄，尿液濃度大約只有血清濃度的25%)
  3. **CNS infections (tigecycline不能穿透BBB)**
- **對下列 G(-) bacilli缺乏抗菌效力：**
  - **a. Pseudomonas aeruginosa**
  - b. Proteus sp (Proteus mirabilis、 Proteus valgaris)
  - c. Providencia spp
  - d. Morganella morganii
  - e. Burkholderia cepacia
- **Bacteriostatic**

Tigecycline: An Expanded Broad Spectrum Antibiotic



Tigecyclin的臨床使用

Tigecycline和Ceftazidime合併使用

Tigecycline對P. aeruginosa缺乏抗菌效力。嚴重Hospital-acquired pneumonia感染症，可能必須與ceftazidime合併使用，抗菌範圍包括抗藥性的各種GPC 、GNB、及其他如anaerobies 、atypical pathogens

〝抗菌範圍Tigecycline + ceftazidime = vancomycin + anti-pseudomonas carbapenem +levofloxacin〞

Tigecyclin的臨床使用，治療嚴重混合感染症 (Hospital-acquired infection)

- Tigecycline + ceftazidime

優點 :適用感染症未併發bacteremia ， septic shock

- tigecycline的組織穿透力好
- 抗菌範圍更廣，(比vancomycin + antipseudomonal carbapenem多增加抗CRAB、antypical pathogen 、anerobes)

缺點：

- 如果感染症併發ceftazidime-resistant GNB bacteremia，可能會發生治療失敗

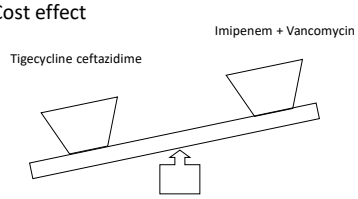
Vancomycin + antipseudomonal carbapenem

- **優點：**
  - 具有足夠的血清濃度治療抗藥性GPC 、GNB bacteremia ， (適用感染症併發septic shock)
- **缺點：**
  - 組織穿透力差，兩者都屬於組織穿透力差的水溶性 (hydrophilic)抗生素
  - Drugs fever?

Is Tigecycline a Tiger?

A golden super combination with Tigecycline with **ceftazidime**?

- Coverage of bacteria spectrum
- Cure rate
- Cost effect

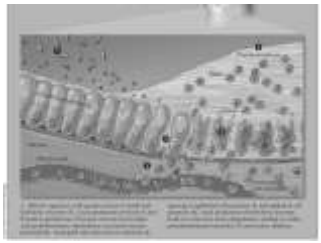


Tigecycline ：

should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria, in order to minimize development of drug-resistant bacteria and maintain drug effectiveness. Tigecycline is not indicated for the treatment of infections due to *Pseudomonas aeruginosa, Proteus spp.*

Clostridium difficile -assciated **Diarrhea (CDAD),** in Adults **(I)**

CMAJ 2004;171(1):51-8 Poutanen SM, Simor AE



- ***Toxin A*** : essential for **invasion.**
- ***Toxin B*** : more potent in causing **inflammation**, ***diarrhea*** !

Pathogenesis in **CDAD** :

Altered flora

↓

Colonization (of toxigenic ***C. difficile*** !)

↓

Elaboration of **toxins**

Clostridium difficile -assciated **Diarrhea** in Adults **(II)**

CMAJ 2004;171(1):51-8 Poutanen SM, Simor AE

Recommended treatment of ***C. difficile*** -associated diarrhea (**CDAD**) in adults

- **First**-line treatment

1. ***Discontinuation of antibiotics if possible.***
2. Metronidazole orally (250 mg 4 times daily, or 500 mg thrice daily) for 10~14 d (give metronidazole intravenously if patients is unable to take medications orally).

- **Alternative** treatment

3. Vancomycin orally (125 mg 4 times daily) for 10~14 d.

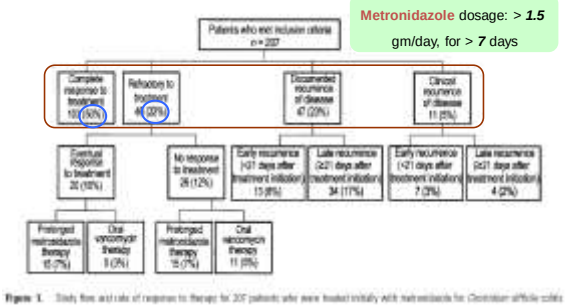
- Treatment of recurrent disease, except above drugs

----- Bacitracin, ***Saccharomyces boulardii*** (or ***Lactobacillus*** GG), cholestyramine (4 gm 3 time daily) as adjunctive medication.

Relatively ***Poor*** Outcome, after Treatment of ***Clostridium difficile*** Colitis with Metronidazole, in Houston, USA, **2004**

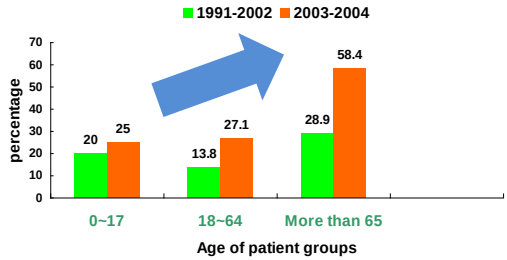
Clin Infect Dis 2005;40:1586-90 Musher DM et al

Metronidazole dosage: > ***1.5*** gm/day, for > ***7*** days



Increasing Risk of Relapse, after Treatment of ***Clostridium difficile*** **Colitis** in Quebec, Canada

Clin Infect Dis 2005;40:1591-7 Pépin J et al



CDAD incidence rate: **>18 year-old groups**, more than **doubled** in 2003-04 (***Significant rise*** !), in which data was censored when the pts died, or **60 days** after the diagnosis of the initial episode (then, using **Cox proportional hazards** model).

Intravenous **Tigecycline** as Adjunctive, or Alternative Therapy for: Severe Refractory ***Clostridium difficile*** Infection

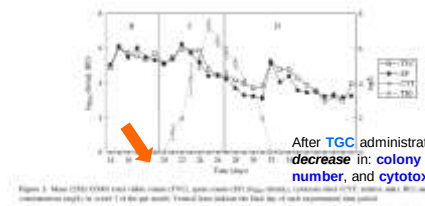
Clin Infect Dis 2009;48:1732-5 Herpers BL et al

Case (Age, sex)	**Underlying Diseases**	Duration of **previous standard tx**	Date of ***relief*** of symptoms, after start of **tigecycline** therapy	**Relapse** withing 3 months ?
1 (60, M)	Cardiothoracic surgery	**Mtz** (5 days); **Vm** (5 days); **Vm** and **Mtz** (32 days)	**Day 3**	**No**
2 (36, F)	Adhesive ileus (ovariectomy)	**Vm** (5 days); **Vm** and **Mtz** (9 days)	**Day 5**	**No**
3 (36, M)	Lung transplant recipient	No standard therapy	**Day 5**	**No**
4 (82, F)	Relaparotomy	**Mtz** (11 days); **Vm** (11 days)	**Day 7**	**No**

The ***fecal*** **tigecycline** concentrations, in **formed stools** (median **5.6** μg/mL; range **3.0-14.1** μg/mL), against **tigecycline** **MIC_{90}** for ***C. difficile*** being **0.06** to **0.25** μg/mL, and: ***not*** induce proliferation, or cytotoxin production of ***C. difficile*** in a gut model !

Tigecycline does ***Not*** induce: Proliferation or Cytotoxin Production by Epidemic ***Clostridium difficile*** strains in a Human Gut Model

J Antimicrob Chemother 2006;58:1062-5. Baines SD et al



After **TGC** administration, gradual ***decrease*** in: **colony counts**, **spore number**, and **cytotoxin titer** !