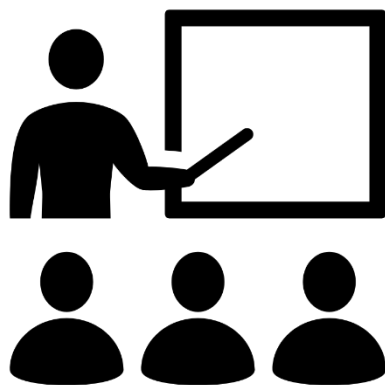# 臨床藥事服務到學術研究及論文撰寫

臺大醫院藥劑部
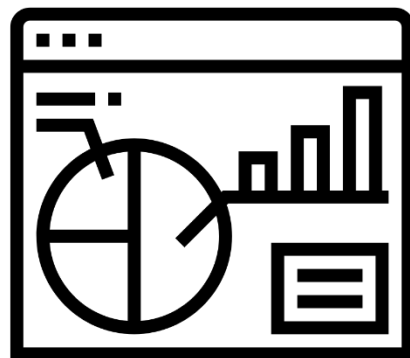## 吳建志組長
20201226

臨床專責藥師

藥事照護

臨床教學

研究發表

A C C P

Position Paper on Critical Care Pharmacy Services

Prepared jointly by the Society of Critical Care Medicine and
the American College of Clinical Pharmacy

Define Fundamental, Desirable, and Optimal pharmacy services

Fundamental pharmacy service

- Dedicated to ICU care
- Evaluate drug therapy, including parenteral nutrition
  - Indication, dosage, allergy, interaction, TDM, monitor efficacy and ADE
- Provide drug information
- Provide drug therapy related education to ICU team members
- Document specific recommendation
- ADR report
- Implement and maintain policies and procedures related to safe and effective use of drug in ICU

Desirable pharmacy service

- **Attend rounds regularly** as a member of multidisciplinary team
  - Medication reconcillation
    - Figure out drug related ICU admissions
  - Provide formal nutrition consultation and response within 24 hours
  - Member of CPR team
  - Provide didactic lectures of critical care to students
- **Training pharmacy students, residents and fellows through experiential critical care rotation**
  - Development and implantation of drug therapy protocol
- **Participate in research and publish reports**

Optimal pharmacy service

- Assist physicians in discussion with patient and family members to make decisions
- Provide formal accredited education sessions for medical staff, students and residents
- Teaching ACLS
- Develop resident and fellowships training program
- Evaluate the impact of guideline or protocol
- Pharmacoeconomic analysis to evaluate pharmacy services
- Secure funds to conduct research
- Reports of research result at regional or national meetings
- Publishes in peer-reviewed pharmacy and medical literature

藥事照護

臨床教學

研究發表
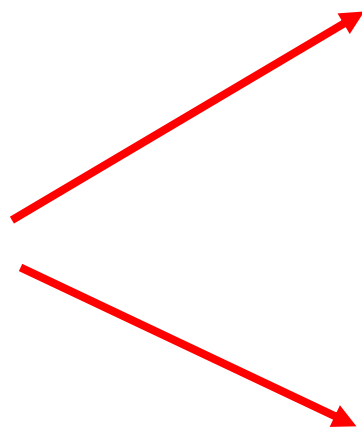
2000 臨床實習：
一個上午跟著臨床藥師至ICU

2005 36週臨床實習：
家醫科、胸腔科、TPN、TDM、感染科、腎臟科、精神科、
和信醫院腫瘤科
一般外科/心臟外科ICU
碩士論文：Vancomycin pharmacokinetic in adult patient
receiving ECMO

2009 NTUH OPD/UDD

2011 UIC臨床藥事照護見習：
一般內科、感染科、神經外科ICU、移植外科

201108 NTUH 內科加護病房專責藥師

2012 MICU APPE preceptor

2015 First SCI publication, a case report

2020 I still work in MICU along with 19 publication (14 SCI paper)
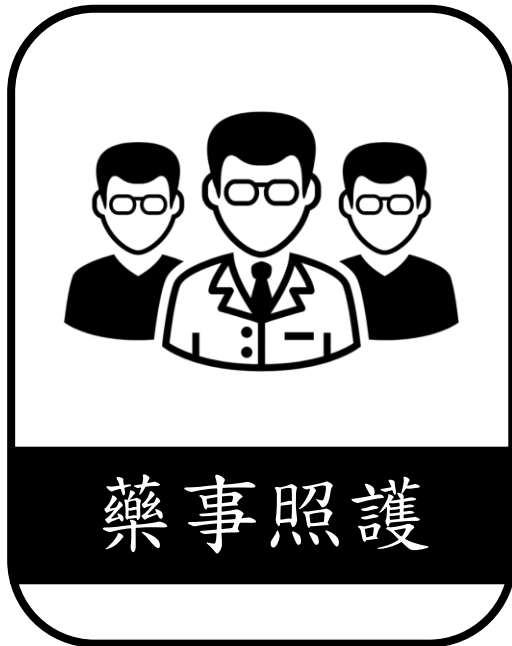
First 2 year as clinical pharmacist

As time goes by

藥事照護
4hr

臨床教學
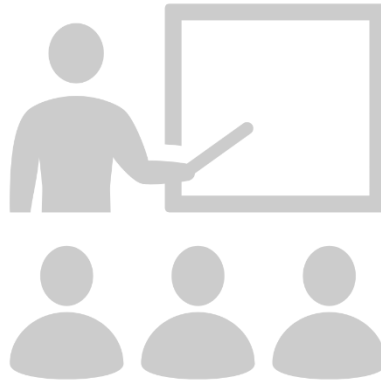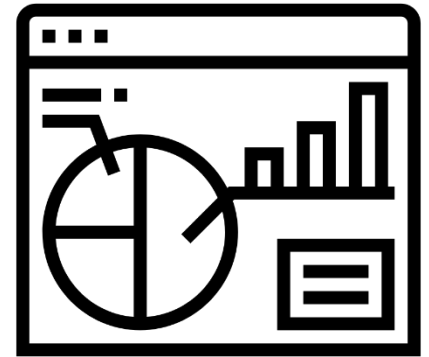**2hr**

研究發表
2hr

As time goes by

藥事照護　　臨床教學　　研究發表

文章類型

- 案例報告
- 案例系列報告
- 回溯性研究
  - 病歷 vs 資料庫
- 前瞻性研究
  - 介入性 vs. 觀察性

Case: MTX intoxication

- 48 y/o male, PMH: psoriasis (MTX 10mg qw) and CKD
- Admitted to ICU due to septic shock s/p vasopressor and CVVH support
  - P. aeruginosa bacteremia
  - Severe neutropenia, diarrhea, mucositis, acute on chronic kidney disease – MTX intoxication
- Question: Could CVVH remove MTX efficiently?
  - Literature:
    - Hemodialysis could remove MTX
    - Only 3 case report for CVVH effect on high dose MTX intoxication
    - No such data on low dose MTX intoxication

Successful Elimination of Methotrexate by Continuous Veno-venous Haemofiltration in a Psoriatic Patient with Methotrexate Intoxication

Chien-Chih Wu[1#], Chih-Fen Huang[1,2#], Li-Jiuan Shen[1–3] and Fe-Lin Lin Wu[1–3]*
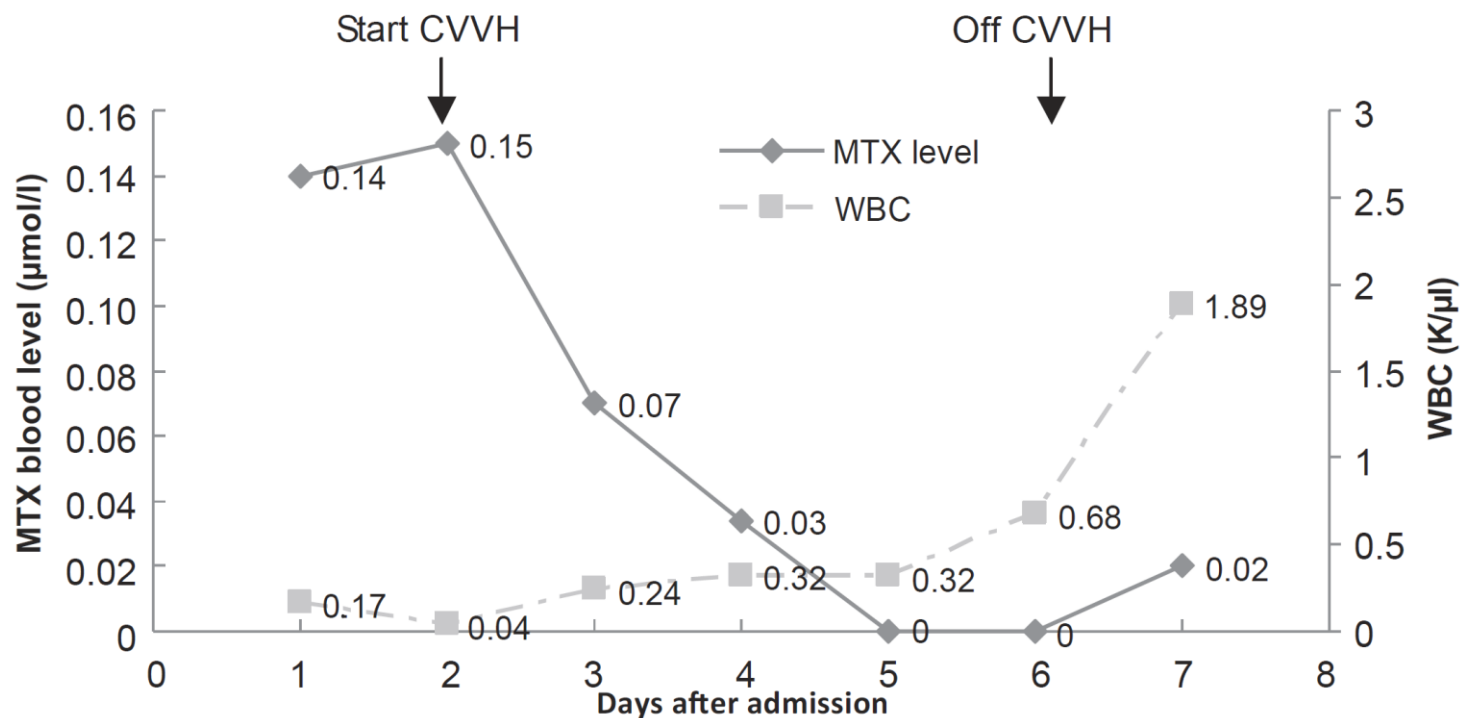
Renal function monitoring of MTX use

Plan：	*Do*：
2013.7.17 One case of low dose MTX related severe pancytopenia was reported. *This event resulted from that renal function was not evaluated recently before initiating MTX*	*Issued Dear Doctor letter to inform the importance of renal function evaluation before low dose MTX use* *Order system automatically check if there is renal function data in recent 3 month if MTX is prescribed.* *Add interaction warning of PPI and penicillin antibiotics*
Act：	*Check*：
Continuous education, esp. for the new colleagues *Actively monitor low dose MTX related pancytopenia*	*No more low dose MTX related pancytopenia afterwards*

藥品交互作用警示

您正開立：**Methotrexate Sodium (Methotrexate 2.5 mg/tab) 1tab PO QD Start on 05/27 15:00**

交互作用結果：Increased risk of methotrexate toxicity
處置方式：Closely monitor MTX levels in patients receiving concomitant PPI and methotrexate. The PPI may have to be discontinued during methotrexate administration.
機轉：Decreased renal elimination of methotrexate by esomeprazole
實證資料：Probable

交互作用品項：
已確認的 Esomeprazole Magnesium (Nexium 40 mg/tab) 1tab PO QDAC1HR Start on 05/16 07:00

☐ 立即停用左列品項

仍需併用請直接按 [繼續]
繼續　取消此筆　回編輯

案例報告-以ADR為例

Naranjo scale

III. 可能性：為評估藥品不良反應，請回答下列問題並勾選適當的答案。

	是	否	不知	給分
1. 以前是否有關於此種不良反應確定的研究報告？	+1	0	0	
2. 此種不良反應是否於服藥之後發生？	+2	-1	0	
3. 當停藥或服用此藥之解藥，不良反應是否減輕？	+1	0	0	
4. 停藥一段時間再重新服用此藥，同樣的不良反應是否再度發生？	+2	-1	0	
5. 有沒有其他原因(此藥品以外)可以引起同樣的不良反應？	-1	+2	0	
6. 當給予安慰劑時，此項不良反應是否也會再度發生？	-1	+1	0	
7. 此藥品的血中濃度是否達到中毒劑量？	+1	0	0	
8. 對此病人而言，藥品劑量與不良反應的程度是否成正向關係？	+1	0	0	
9. 病人過去對同樣或類似藥品是否也產生同樣的不良反應？	+1	0	0	
10.此項不良反應是否有客觀的證據？	+1	0	0	
			總分	

Acute Hepatotoxicity of Intravenous Amiodarone: Case Report and Review of the Literature
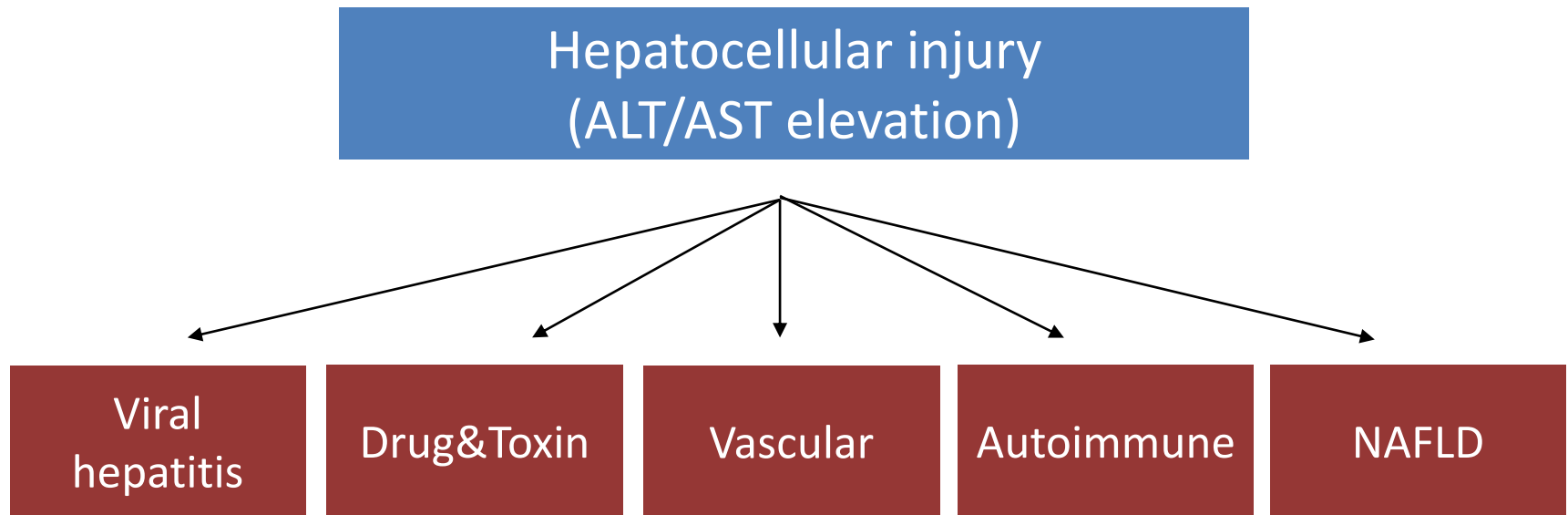
Chia-Chi Chen, MSCP[1] and Chien-Chih Wu, MSCP[1,2]*

Table 1. Clinical course after intravenous and oral amiodarone use.

Day	Dosage	AST (<37 U/L)	ALT (M < 41 U/L)	T-bil (0.2–1.2 mg/dL)	ALP (60–220 U/L)	GGT (0–52 IU/L)
−2	100 mg, QD PO	—	—	—	—	—
−1	100 mg, QD PO	29	77	—	—	—
0	150 mg once IF	—	—	—	—	—
1	1350 mg, QD cIF	—	—	—	—	—
2	100 mg, PO for 1 dose	4374	>2500	0.77	108	85
3	—	1042	>2500	0.97	108	99
4	—	480	2200	0.81	—	—
6	—	186	1101	0.82	—	—
9	—	37	419	—	—	—
11	—	23	204	0.74	—	—
14	—	20	88	—	—	—
18	100 mg, BID PO	—	—	—	—	—
19	100 mg, BID PO	25	4	0.76	—	—
23	100 mg, BID PO	26	4	—	—	—
53	100 mg, BID PO	29	17	—	—	—

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransaminase; BID, twice a day; cIF, continuous infusion; D0, the start day of intravenous amiodarone; GGT, gamma-glutamyl transpeptidase; PO, orally; QD, everyday; T-bil, total bilirubin.

Acute Hepatotoxicity of Intravenous Amiodarone: Case Report and Review of the Literature

Chia-Chi Chen, MSCP[1] and Chien-Chih Wu, MSCP[1,2]*

Acute Hepatotoxicity of Intravenous Amiodarone: Case Report and Review of the Literature

Chia-Chi Chen, MSCP[1] and Chien-Chih Wu, MSCP[1,2]*

However, tremendous AST/ALT elevation was incidentally found (Table 1) within 24 hours after IV amiodarone use. Amiodarone was discontinued immediately because of its possible hepatotoxicity. Hepatitis B viral load were also checked to rule out hepatitis B flare up. On the following days, AST/ALT improved gradually. The hepatocellular injury was probably because of IV amiodarone. Hepatitis B flare up was not likely because of low viral load (36 IU/mL). Ischemia-related liver injury was ruled out due to no shock event during this period and no other organ damage. Aspirin, clopidogrel, mexiletine, and isosorbide mononitrate were used simultaneously; however, all these agents did not show obvious hepatotoxicity.

Acute Hepatotoxicity of Intravenous Amiodarone: Case Report and Review of the Literature

Chia-Chi Chen, MSCP[1] and Chien-Chih Wu, MSCP[1,2]*

Table 2. Case reports summary of intravenous amiodarone-related hepatitis.

Reference	Year	Age (yr)	Sex	Underlying disease	Indication	Onset	AST/ALT (U/L)	T-bil (mg/dL)/ ALP (U/L)	Time to recovery	Oral amiodarone rechallenge
Gregory et al[10]	2002	74	F	N/A	VT	<1 d	1099/759	N/A	6 d	(+)
Ratz Bravo et al[8]	2005	66	F	CAD, HF	AF	<1 d	2454/3822	1.52/47	>14 d	(−)
		73	F	HTN, DM, hyperlipidemia	AF	<1 d	12,795/5975	1.05/201	>14 d	(−)
		57	M	CAD, VHD, HF	AF	<1 d	1901/1590	2.51/63	25 d	(+)
Maker et al[11]	2005	54	M	Burn	AF	5 d	739/1303	N/A	28 d	(+)
Rao et al[12]	2012	44	M	Old inferior infarct, DCMP, HF, HTN	AF	<1 d	–/4578	2.63/194	10 d	(−)
Kickers et al[13]	2012	5 mo	F	Down syndrome, congenital heart defect	Junctional ectopic tachycardia	4 d	1212/1056	4.4/–	>14 d	(−)
Nasser et al[14]	2013	88	F	Hypothyroidism, HTN, depression	AF	<1 d	1881/1048	–/174	7 d	(−)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransaminase; AF, atrial fibrillation; CAD, coronary artery disease; DCMP, dilated cardio-myopathy; DM, diabetes mellitus; F, female; HF, heart failure; HTN, hypertension; M, male; N/A, not available; T-bil, total bilirubin; VHD, valvular heart disease.

Acute Hepatotoxicity of Intravenous Amiodarone: Case Report and Review of the Literature

Chia-Chi Chen, MSCP[1] and Chien-Chih Wu, MSCP[1,2]*

Abstract

Amiodarone is a class III antiarrhythmic drug widely used for the treatment of both supraventricular and ventricular arrhythmias in intensive care unit. Hepatotoxicity of amiodarone is usually mild and delayed onset. Acute hepatotoxicity is a rare side effect and usually correlated to intravenous form use. In this case, acute hepatocellular injury occurred within 24 hours after the administration of intravenous amiodarone. Liver enzyme significantly improved after holding intravenous amiodarone use. Because ventricular arrhythmia persisted and side effects occurred to alternative therapy, low dose of oral amiodarone was resumed and hepatotoxicity did not occur afterward. Acute hepatotoxicity of intravenous amiodarone is possibly related to polysorbate 80, the solubilizer of amiodarone infusion or higher dose. As a result, when intravenous amiodarone is prescribed, closely monitoring liver enzyme is highly suggested. If acute hepatitis takes place secondary to intravenous amiodarone, oral therapy should not be resumed afterward. If there is no alternative treatment, lower dose of oral amiodarone (≤ 200 mg/d) could be tried and should monitor liver function regularly.

Keywords: amiodarone, hepatotoxicity, adverse drug reaction

決定在期刊或研討會要求，注意字數、格式

社團法人臺灣臨床藥學會
Taiwan Society of Health-System Pharmacists

👤 登入　🔗 外部連結　🌐 English

請輸入關鍵字　　查詢

關於學會　審查案件申請　活動訊息　臨床藥學雜誌　公告資訊　年會專區　研究計畫　國際事務

共同提升藥學專業服務

臨床藥學雜誌/雜誌相關公告

臨床藥學雜誌　　雜誌相關公告

雜誌相關公告
投稿連結
已出刊文章

107
07.10　　**臺灣臨床藥學雜誌投稿規則及表格**

–摘要（Abstract）：

(1) 除短文之外，均須附上中文及英文摘要；中文摘要限 500 字(含)以內，英文摘要限 250 字(含)以內。

(2) 原著摘要應依序列出子標題分段繕打：目的 (Objective)、方法 (Methods)、結果 (Results)、結論 (Conclusions) 等。

(2) 案例報告：引言、案例報告、討論等順序繕打。本文加誌謝總字數以 3,000 字為限。

(3) 綜合評述：本文形式不拘。本文加誌謝總字數以 5,000 字為限。

(4) 評論：本文形式不拘。本文加誌謝總字數以 5,000 字為限。

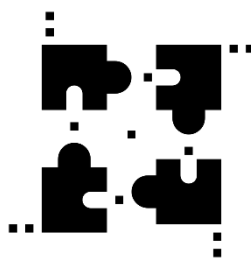(5) **專題報導：僅以邀稿為限。**
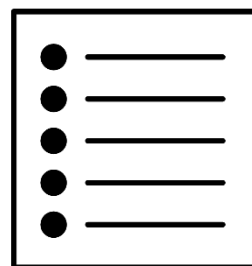
(6) 短文：引言、方法、結果、討論。本文加誌謝總字數以 1,000 字為限。
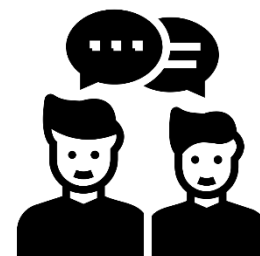
研究從無到有的過程

題目發想　　文獻回顧　　研究方法資料收集　　結果　　討論與結論

研究從無到有的過程

題目發想

- 文獻建議與實際於臨床使用的差異
- 目前文獻的缺口
- 專科臨床經驗越多，越能發現該專科重要未解的臨床問題
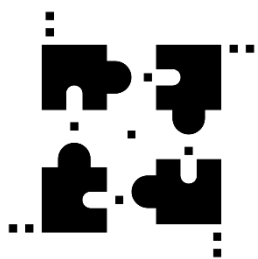
文獻回顧　研究方法 資料收集　結果　討論與結論

What's new, What's important

研究從無到有的過程

研究方法
資料收集

- 尋找相關背景老師或統計諮詢進行討論以確認研究方法
- 臨床藥師提供需要收集的欄位資訊
- 人力配置進行資料收集及處理的工作

文獻回顧　　　資料收集　　　結果　　　討論與結論

The Effect of Different Carbapenem Antibiotics (Ertapenem, Imipenem/Cilastatin, and Meropenem) on Serum Valproic Acid Concentrations

Chien-Chih Wu, MSCP,*† Tsung-Yu Pai, PharmD,* Fei-Yuan Hsiao, PhD,*†‡ Li-Jiuan Shen, PhD,*†‡ and Fe-Lin Lin Wu, PhD*†‡§

- ## Idea from
  - 某一段時間遇到好幾個使用valproic acid的病人，同時使用meropenem，濃度真的降低的很顯著。

- ## Question
  - 不同carbapenem對valproic acid的濃度影響程度是否不同?
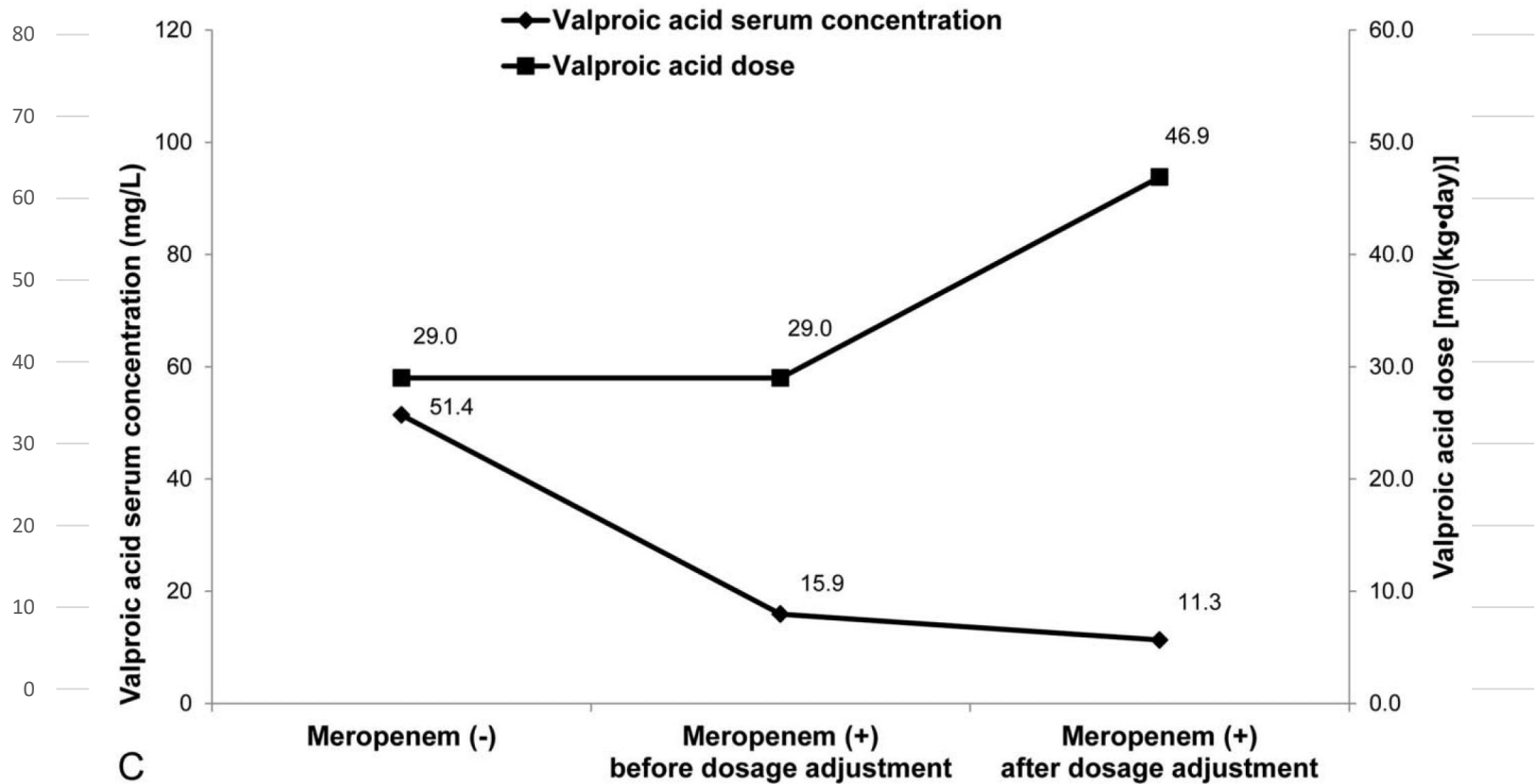 - 多快發生?
  - 增加劑量是否可以克服這個交互作用?

The Effect of Different Carbapenem Antibiotics (Ertapenem, Imipenem/Cilastatin, and Meropenem) on Serum Valproic Acid Concentrations

Chien-Chih Wu, MSCP,*† Tsung-Yu Pai, PharmD,* Fei-Yuan Hsiao, PhD,*†‡ Li-Jiuan Shen, PhD,*†‡ and Fe-Lin Lin Wu, PhD*†‡§
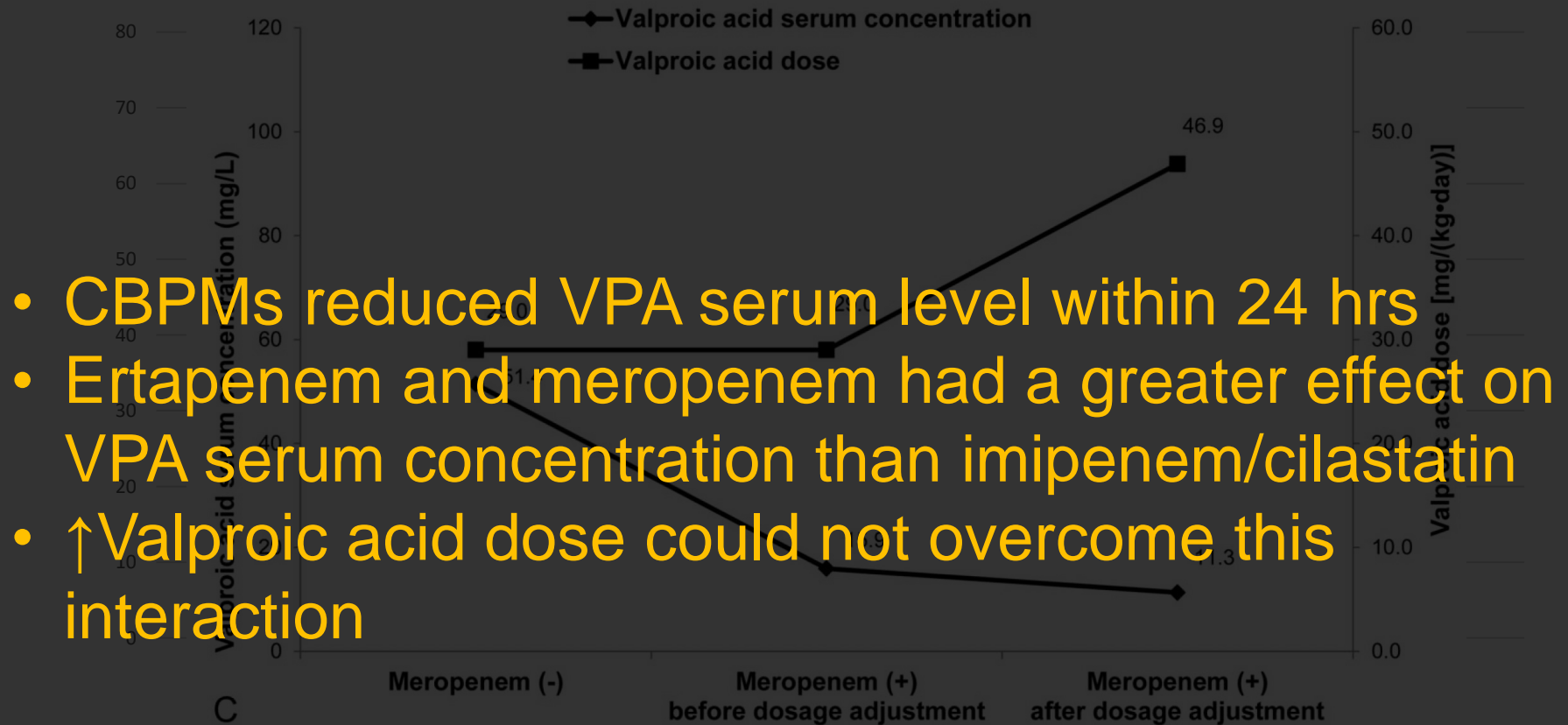
The Effect of Different Carbapenem Antibiotics (Ertapenem, Imipenem/Cilastatin, and Meropenem) on Serum Valproic Acid Concentrations

Chien-Chih Wu, MSCP,*† Tsung-Yu Pai, PharmD,* Fei-Yuan Hsiao, PhD,*†‡ Li-Jiuan Shen, PhD,*†‡ and Fe-Lin Lin Wu, PhD*†‡§

- CBPMs reduced VPA serum level within 24 hrs
- Ertapenem and meropenem had a greater effect on VPA serum concentration than imipenem/cilastatin
- ↑Valproic acid dose could not overcome this interaction

How to finish this study?

- 病歷回顧收集相關資料
  - 共88個病人，最後符合條件的共52個病人
- 相對簡單的統計分析
  - Differences between CBPMs' groups were determined by the analysis of variance (ANOVA). Scheffe method was used as a post hoc analysis for the differences between groups.

Lexicomp® Drug Interactions

Add items to your list by searching below.

Enter item name

ITEM LIST

Clear List   Analyze

⊖ Valproic Acid and Derivatives

⊖ Meropenem

Display complete list of interactions for an individual item by clicking item name.

NOTE: This tool does not address chemical compatibility related to I.V. drug preparation or administration.

interaction in a cirrhotic patient.[23] The reason for an absent interaction in this case is uncertain, though it is possible that impaired hepatic glucuronidation and biliary drug secretion due to the patient's advanced liver disease led to decreased valproic acid clearance, countering the effects of the carbapenem.

Footnotes

1. Huang CR, Lin CH, Hsiao SC, et al. Drug interaction between valproic acid and carbapenems in patients with epileptic seizures. *Kaohsiung J Med Sci*. 2017;33(3):130-136. [PubMed 28254115]

2. Miranda Herrero MC, Alcaraz Romero AJ, Escudero Vilaplana V, et al. Pharmacological interaction between valproic acid and carbapenem: what about levels in pediatrics? *Eur J Paediatr Neurol*. 2015;19(2):155-161. [PubMed 25578527]

3. Haroutiunian S, Ratz Y, Rabinovich B, Adam M, Hoffman A. Valproic acid plasma concentration decreases in a dose-independent manner following administration of meropenem: a retrospective study. *J Clin Pharmacol*. 2009;49(11):1363-1369. [PubMed 19773524]

4. Wu CC, Pai TY, Hsiao FY, Shen LJ, Wu FL. The effect of different carbapenem antibiotics (ertapenem, imipenem/cilastatin, and meropenem) on serum valproic acid concentrations. *Ther Drug Monit*. 2016;38(5):587-592. [PubMed 27322166]

5. Nagai K, Shimizu T, Togo A, et al. Decrease in serum levels of valproic acid during treatment with a new carbapenem, panipenem/betamipron. *J Antimicrob Chemother*. 1997;39(2):295-296. [PubMed 9069562]

6. Yamagata T, Momoi MY, Murai K, et al. Panipenem-betamipron and decreases in serum valproic acid concentration. *Ther Drug Monit*. 1998;20(4):396-400. [PubMed 9712464]

7. De Turck BJ, Diltoer MW, Cornelis PJ, et al. Lowering of plasma valproic acid concentrations during concomitant therapy with meropenem and amikacin. *J Antimicrob Chemother*. 1998;42(4):563-564. [PubMed 9818768]

The ratio of pre-dialysis vancomycin trough serum concentration to minimum inhibitory concentration is associated with treatment outcomes in methicillin-resistant *Staphylococcus aureus* bacteremia

Chien-Fang Fu[1], Jiun-Da Huang[1], Jann-Tay Wang[2], Shu-Wen Lin[1,3,4], Chien-Chih Wu[1,3]*

- ## Idea from
  - 原本是想看在洗腎病人vancomycin dose 7-10 mg/kg TIW，洗腎前濃度的分佈，但是之前已經有很多人做過類似的研究，無新意。
  - 2009 vancomycin guideline
    - For a pathogen with an MIC of 1 mg/L, the minimum trough concentration would have to be at least 15 mg/L to generate the target AUC:MIC of 400.
    - 引用的原始paper exclude洗腎的病人，所以在洗腎病人濃度和臨床療效尚無相關研究

Result

ROC Curve
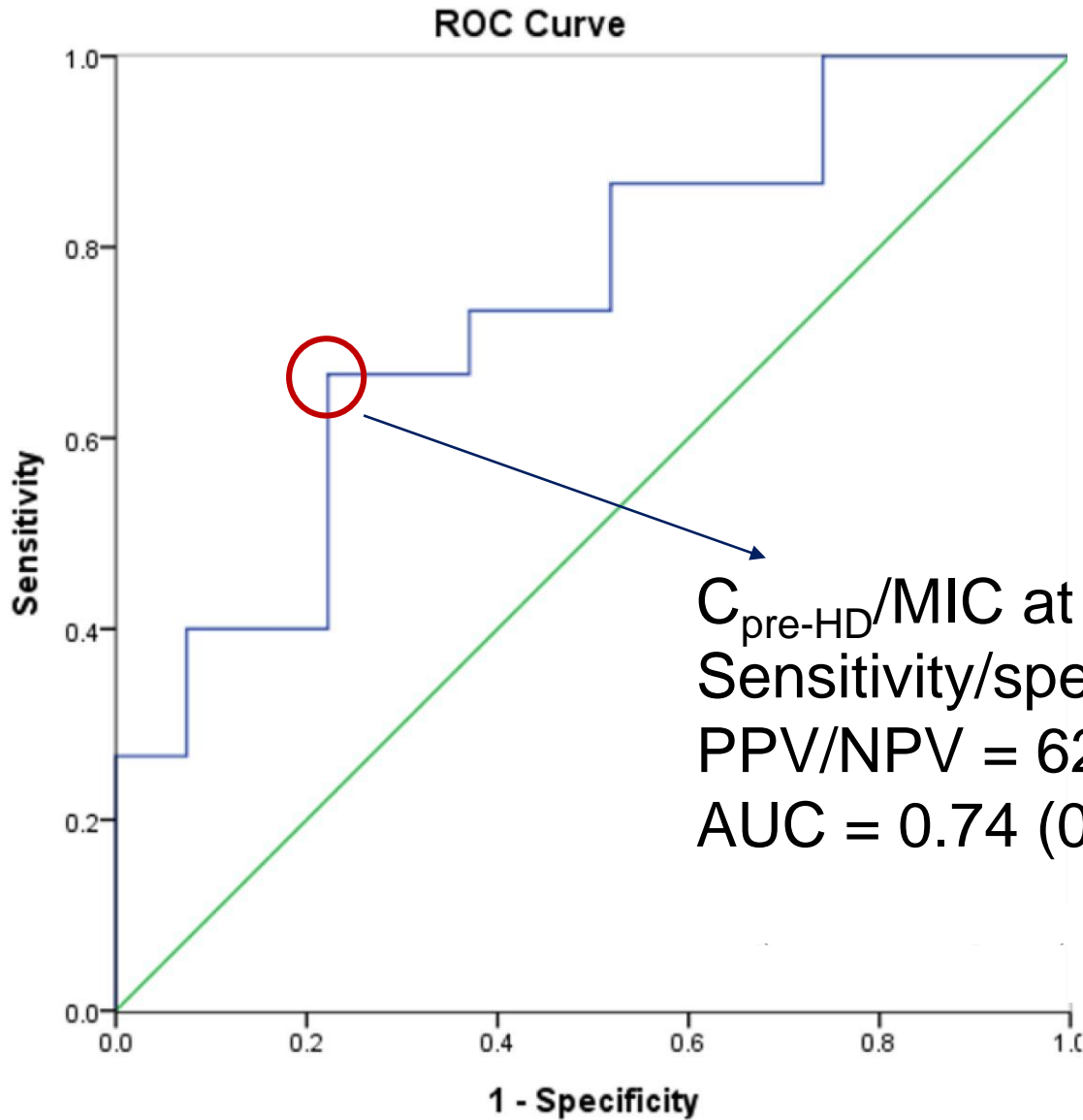
C_{pre-HD}/MIC at the cut-off value of 18.6
Sensitivity/specificity = 67/78 %
PPV/NPV = 62.5/81 %
AUC = 0.74 (0.58, 0.90)

How to finish this study?

- 資料庫篩選病人
- 病歷回顧收集相關資料
  - 共65個病人，最後符合條件共42個病人
- 統計分析
  - 連續變數: Student t test; Mann Whitney U test
  - 類別變數: Fisher exact test/Chi-square test
  - The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off point of Cpre-HD/MIC, which had the maximum Youden index.
  - Logistic regression

2020 Therapeutic monitoring of vancomycin in adult patients

Renal Disease and Renal Replacement Therapies

Intermittent hemodialysis. Despite the common use of vancomycin in patients receiving hemodialysis, there are few published outcome studies that provide guidance on the optimal PK/PD targets in this population. Previously published drug dosing recommendations generally targeted a predialysis serum concentration, even though other PD targets may be more appropriate. Predialysis vancomycin concentration to MRSA MIC ratios of >18.6 have been associated with improved bacteremic patient outcomes, suggesting that serum concentration monitoring is essential throughout the course of therapy.[128] Dosing to achieve predialysis vancomycin concentrations of 10 to 20 mg/L, as has been done clinically,[129] results in mean AUC_{24} values ranging from 250 to 450 mg·h/L, with be based on serum concentration monitoring.[132]

Vancomycin dosing in patients with acute or chronic kidney failure has transformed over time due to the changes in dialysis technology and techniques.[133] Older (pre-1990s) hemodialyzers were not very permeable to large molecules. Vancomycin (with a molecular weight of 1,450 Da) was not considered "dialyzable" because it poorly crossed the hemodialysis membranes of the era. Indeed, even today's vancomycin package insert, based on PK studies conducted in the 1980s, states that "vancomycin is poorly removed by dialysis."[134] As hemodialysis membrane technology has improved, dialyzers have become far more permeable. Vancomycin is cleared substantially by contemporary high-permeability hemodialyzers[135,136]; consequently, vancomycin dosing strategies have changed substantially per day, and holding a dialysis chair for 60 to 90 additional minutes while vancomycin infuses into a patient is not cost-effective. Indeed, it is more cost-effective to infuse "extra" vancomycin during the hemodialysis session to compensate for intradialytic loss than it is to keep a dialysis unit open later to allow vancomycin infusions. Intradialytically infused vancomycin results in reduced delivery of drug to the patient, similar to a first-pass phenomenon. The extent of intradialytic drug removal is variable and depends on patient and dialysis system factors, the most important of which is dialyzer membrane permeability.[135,137-139] Approximately 20% to 40% of an intradialytically administered vancomycin dose is removed by the simultaneous hemodialysis, with the highly permeable dialyzers tending to the higher end of this range.[137,140,141]

Maintenance dosing strategies that do not provide a dose with every hemodialysis session (eg, a maintenance

Suggestion:
1. Maintaining pre-dialysis level 15-20 mg/L
2. Pre-dialysis concentration monitoring should be performed not less than weekly

Manuscript Sections

- Title
- Author
- Abstract/Summary
- Introduction
- Material and methods
- Results
- Discussion
- Conclusions
- Reference

Manuscript Sections

- Title
  - 一看就知道內文主要在講什麼，盡量越短越好

抗生素併用引起之急性腎衰竭

VS

Vancomycin與piperacillin/tazobactam併用引起之急性腎衰竭

Authors

- ICMJE criteria
  - 提出研究問題、研究設計、獲取資料、分析資料、解讀資料
  - 撰寫初稿、修改文章、送出完稿
  - 對研究內容負責，確認研究的完整性與真實性
- Author list
  - First author (第一作者), corresponding author(通訊作者)
  - 其他依貢獻程度排序
- 不符合以上條件，列在致謝(acknowledgement)

ICMJE: the international committee of medical journal editors

Introduction

- 目前這個主題的文獻回顧
  - 甚麼是目前已知
    - 引述重點，不需要太細節
  - 甚麼是目前未知(knowledge gap)
  - 盡量引用近代的文獻(5年內)
- 研究的假說及目的

- 讀者: 為什麼要做這個研究，重要性在哪，有甚麼新意

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common pathogen which causes infections, especially among patients who undergo dialysis.[1] Vancomycin is an antibiotic glycopeptide which kills bacteria by inhibiting cell wall synthesis, and it is the first line treatment for MRSA infection if minimum inhibitory concentration (MIC) is lower than 1 mg/L [2]. The clinical efficacy of vancomycin is best predicted by the area under the curve over 24 hours (AUC_{24}) to the MIC ratio, and a target AUC_{24}/MIC ratio of ≥ 400 is recommended by the Infectious Diseases Society of America (IDSA) Practice Guideline[2–4]. The trough serum concentration (C_{trough}) of vancomycin is recommended as a surrogate for the AUC_{24} and should be maintained between 15–20 mg/L to achieve an AUC_{24}/MIC ≥ 400 when MIC is ≤ 1 mg/L[2, 5].

目前已知

Introduction

mg/L[2, 5]. However, among previous studies that investigated the association between vancomycin AUC_{24}/MIC or C_{trough} and treatment outcome, few examined renal failure patients who received renal replacement therapy such as hemodialysis (HD)[3, 4, 6, 7]. The immune function was changed in renal failure patients, which may affect treatment outcome than that in general population.[8] Therefore, the AUC_{24}/MIC or C_{trough} target may be different in this vulnerable population. As a result, current vancomycin dosing regimen for HD patients relies mainly on extrapolation or modeling.[9] Although pre- or post-HD serum concentration monitoring has been adopted as a common clinical practice for years in vancomycin-treated patients with renal failure under HD, the best time of sampling remains controversial[10]. Moreover, previous studies all focused on developing specific dosing protocols in renal failure patients to achieve the target vancomycin serum concentration of 10–20 mg/L[11–15]. Nonetheless, evidence is still lacking to show any correlation between pre-dialysis vancomycin trough serum concentration (C_{pre-HD}) and the clinical outcomes in this patient population. Our aim is to investigate the relationship between C_{pre-HD} and treatment outcomes of MRSA bacteremia in patients undergoing HD.

目前未知、研究假說、目的

Material and methods (1)

- 2個基本問題
  - 你用甚麼做的(病歷回顧/資料庫; 收集甚麼欄位)
  - 你怎麼做出來的(統計分析)
- 讓別人可以重現你的研究
- 論文寫作可第一個寫的地方，邊作邊寫

Material and methods (2)

- 架構
  - 案例納入、排除條件
    - 涉及到病人資料，應有倫委會通過說明
  - 資料收集或介入
  - 試驗相關細節
  - 結果定義
  - 統計與資料分析
    - 包含使用的統計軟體(Excel)

Material and methods (2)

Material and methods

This retrospective study was conducted in the National Taiwan University Hospital (NTUH), which is a tertiary medical center with a 2600-bed capacity in northern Taiwan., and patients profiles during January 2013 to June 2016 of the Integrated Medical Database (NTUH-iMD) was used for patient enrollment. This study had been approved by the Research Ethics Committee of NTUH (201602044RINB). Adult patients ($\geq$ 20 yrs) with chronic renal failure undergoing HD three times per week were included if they had documented MRSA bacteremia, and received vancomycin treatment within 72 hours after the blood sample from which the MRSA was first isolated. MRSA bacteremia was defined as at least one set of blood culture that was collected when systemic inflammatory response syndrome was present and yielded MRSA.

Patients were excluded for missing C_{pre-HD} measurements during the treatment course, vancomycin use less than a week, absence of following blood cultures collected after vancomycin treatment, ever receiving other antibiotics for MRSA treatment (such as daptomycin, linezolid, teicoplanin and tigecycline) within 7 days before vancomycin treatment, receiving continuous renal replacement therapy (CRRT) during vancomycin treatment or daily urine output over than 400 mL.

研究設計、納入/排除條件、倫理議題

Material and methods

The dosing regimen of vancomycin for patients under HD in our institution was 15–20 mg/kg as a loading dose (LD), followed by 7–10 mg/kg after each HD as maintenance doses (MD). The sampling time of C_{pre-HD} was within one hour before the third HD session since giving one LD and two MD. The vancomycin serum concentrations were measured by a chemiluminescent microparticle immunoassay (ARCHITECT i2000SR immunoassay analyzer, Abbott Laboratories, Abbott Park, Illinois, USA). The limit of detection (sensitivity) was 0.24 mg/L, and the coefficients of variation at 7.0, 35.0, and 75.0 mg/L were < 5%. For hemodialysis, the blood and dialysate flow rates were set at 200 and 500 mL/min, respectively. The dialysis lasted 4 hour each time and the dialyzers used were F6HPS, FX60, FX80, or FX100 by nephrologist's decision (Fresenius Medical Care, Bad Homburg, Germany).

試驗相關細節

Material and methods

A standardized case report form was used to collected data including demographic characteristics (sex, age, height, and weight), the Charlson Comorbidity Index (CCI) and underlying diseases, sources and sites of infection (based on medical records and culture sampling sites), subsequent blood cultures results, immunosuppressant usage (i.e. prednisolone $\geq$ 10mg/day or other corticosteroids of equivalent potency, calcineurin inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, azathioprine, and mycophenolate mofetil), catheterization, catheter removal, vancomycin doses and duration of treatment, C_{pre-HD}, MIC of vancomycin for MRSA, concurrent antibiotics usage, shock status (use of vasopressors or inotropics), and 30-day mortality. The MIC of vancomycin for the first isolate was determined by the broth microdilution method according to the Guidelines of the Clinical and Laboratory Standards Institute (CLSI) except for two MIC of vancomycin that was determined by E-test according to the manufacturer's instruction.[16] Because AUC_{24} and C_{pre-HD} are highly correlated in patients receiving HD, we calculate C_{pre-HD}/MIC as a surrogate of AUC_{24}/MIC to evaluate its effect on treating MRSA bacteremia.[9]

資料欄位收集、資料定義

Material and methods

Treatment failure was defined as persistent bacteremia after $\geq$ 7 days of vancomycin treatment, or recurrent MRSA infection within 30 days after the first negative conversion of blood culture.[2] 結果定義

Data were described as mean ± standard deviation or number with percentage. The two-tailed independent t test was used for continuous data, and either Chi-square or Fisher's exact test was used for categorical data. A p-value of 0.05 or lower was considered statistically significant. The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off point of C_{pre-HD}/MIC, which had the maximum Youden index. The statistical analysis was performed by SPSS 18 (SPSS Inc, Chicago, Illinois, USA). 統計分析

Results

- 呈現數據
  - 附上統計結果如p value、95%信賴區間
- 善用圖表
  - 圖表可放入大量資訊
  - 多數讀者只看abstract、圖、表
  - 圖表的順序應和在敘述中出現的次序一致
  - 每張圖表的字體要一致
  - 定義縮寫，適當命名圖表標題
  - 以TIFF檔存取(lossless file)；JPEG (lossy file)
- 其他較次要的訊息或分析可考慮放入補充資料 (Supplemental Material)或附錄(Appendices)

Results

Sixty-five HD patients who received vancomycin due to MRSA bacteremia were initially enrolled. Twenty-three patients were excluded for lacking following blood culture collected (n = 8), missing pre-dialysis serum level data (n = 3), using other antibiotics within 7 days before vancomycin treatment (n = 7), or receiving CRRT (n = 5) during vancomycin treatment. Forty-two patients were available for the final analysis.

Fifteen patients (36%) were successfully treated, and the other 27 were classified as treatment failure (64%). In the treatment failure group, 25 patients had persistent bacteremia, and 2 had recurrent MRSA infection, which two weeks course of antibiotics was completed before. Although there were no significant differences in baseline demographics, underlying disease, sources of bacteremia, or vancomycin regimens between the success and failure group, more patients received immunosuppressants in treatment failure group (Table 1). Catheters were all removed in both groups after confirming it as infection source. C_{pre-HD} values were not significantly different between the success and failure groups (17.40 ± 4.55 vs. 15.22 ± 4.24 mg/L, $p = 0.139$) (Table 2). However, C_{pre-HD}/MIC was significantly higher in the success group compared to that of the failure group (22.80 ± 10.90 vs. 14.94 ± 6.11, $p = 0.019$). There was also no significant difference in 30-day mortalities between the success and failure groups (11% vs 19%, $p = 0.666$).

In the treatment failure group, the antibiotic agent was switched from vancomycin to daptomycin in 16 patients and linezolid in 1 patient based on physicians' judgement and clinical situations. MRSA was eventually eradicated in 12 of the 16 patients, and 7 of them had negative blood culture within 7 days of daptomycin treatment. Only two patients failed to achieve blood culture conversion under daptomycin, and 2 patients did not have subsequent blood culture collected after daptomycin use.

The prediction power of C_{pre-HD}/MIC for treatment outcome was evaluated using the ROC curve analysis. The optimal cut-off value of C_{pre-HD}/MIC was 18.6, with the sensitivity of 67% and the specificity of 78%. The area under the ROC curve was 0.74 (95% confidence interval: 0.58–0.90, $p = 0.011$) (Fig 1), and the positive predictive value and negative predictive value were 62.5% and 81%, respectively.

Table 1. Clinical characteristics and vancomycin dose, classified by vancomycin treatment outcomes.

	Total patients (N = 42)	Success group (N = 15)	Failure group (N = 27)	*p* value
Age	69.00 ± 14.81	71.80 ± 13.23	67.44 ± 15.63	0.346
Height (cm) (mean ± standard deviation)	159.57 ± 8.10	160.09 ± 6.83	159.29 ± 8.84	0.747
Weight (kg) (mean ± standard deviation)	56.23 ± 9.597	59.25 ± 9.66	54.55 ± 9.32	0.137
Male sex	20 (48)	5 (33)	15 (56)	0.209
Underlying disease				
Charlson Comorbidity Index (mean ± SD)	4.71 ± 2.04	4.53 ± 1.51	4.81 ± 2.30	0.636
Cardiovascular disease	28 (67)	12 (80)	16 (59)	0.306
Chronic liver disease	4 (10)	2 (13)	2 (7)	0.608
Diabetes mellitus	21 (50)	8 (53)	13 (48)	1.000
Malignancy	5 (12)	0 (0)	5 (19)	0.142
Neurological disease	9 (21)	2 (13)	7 (26)	0.451
Peptic ulcer disease	14 (33)	5 (33)	9 (33)	1.000
Connective tissue disease	1 (2)	0 (0)	1 (4)	1.000
Neutropenia	0 (0)	0 (0)	0 (0)	
Septic shock	14 (33)	5 (33)	9 (33)	1.000
Polymicrobial bacteremia	11 (26)	3 (20)	8 (30)	0.717
Acinetobacter baumannii	2 (5)	1 (7)	1 (4)	
Burkholderia cepacia complex	1 (2)	1 (7)	0 (0)	
Enterococcus faecalis	2 (5)	1 (7)	1 (4)	
Enterococcus faecium	1 (2)	0 (0)	1 (4)	
Escherichia coli	3 (7)	1 (7)	2 (7)	
Klebsiella pneumoniae	3 (7)	0 (0)	3 (11)	
Pseudomonas aeruginosa	1 (2)	0 (0)	1 (4)	
Serratia marcescens	1 (2)	1 (7)	0 (0)	
Stenotrophomonas maltophilia	1 (2)	0 (0)	1 (4)	
Immunosuppressants use	6 (14)	0 (0)	6 (22)	0.056
MRSA bacteremia source				0.981
Bone and joint	0 (0)	0 (0)	0 (0)	
Catheter-related	11 (26)	4 (27)	7 (26)	
Endocarditis	2 (5)	0 (0)	2 (7)	
Pneumonia	6 (14)	2 (13)	4 (15)	
Surgical wound or skin and soft tissue	6 (14)	2 (13)	4 (15)	
Unknown	17 (41)	7 (47)	10 (37)	
Vancomycin MIC (mg/L) (mean ± SD)				0.075
< 0.5	7 (16)	5 (33)	2 (7)	
1	29 (69)	9 (60)	20 (74)	
1.5	2 (5)	1 (7)	1 (4)	
2	4 (10)	0 (0)	4 (15)	
Concurrent antibiotics	31 (74)	10 (67)	21 (78)	0.481
Penicillin group	6 (14)	2 (13)	4 (15)	
Cephalosporin group	24 (57)	6 (40)	18 (67)	
Carbapenem group	8 (19)	1 (7)	7 (26)	
Fluoroquinolone	1 (2)	0 (0)	1 (4)	
Trimethoprim/sulfamethoxazole	3 (7)	2 (13)	1 (4)	
Aminoglycoside	1 (2)	0 (0)	1 (4)	
Colistin	1 (2)	0 (0)	1 (4)	
Antifungal agents	1 (2)	0 (0)	1 (4)	
	Total patients (N = 42)	**Success group (N = 15)**	**Failure group (N = 27)**	***p* value**
Antiviral agents	2 (5)	0 (0)	2 (7)	

SD: standard deviation. MRSA: methicillin-resistant *Staphylococcus aureus*.

Discussion

- 這篇文章的意義和重要性
- 解讀結果
- 和之前的文獻作比較，甚麼原因造成結果不同
  - 可能是收入族群、定義或分析方法不同
- 未來的研究方向
- 若出現不預期的結果，推敲可能的原因，形成下一個研究的假說
- 簡明扼要，寫太多可能會使reviewer沿生其他你從未想過的問題
- 提出研究限制

Discussion

This is the first study known to the authors focusing on the correlation between the C_{pre-HD} of vancomycin and the treatment outcomes for MRSA bacteremia in dialysis patients. The relationship between vancomycin C_{trough}, AUC_{24}/MIC, and the clinical outcomes for MRSA infection has been well studied in the general population, and that C_{trough} of 15 mg/L or higher, corresponded to the $AUC_{24}/MIC > 400$, was recommended by the IDSA guideline[2–7, 17, 18]. This standard was extrapolated for patients who received renal replacement therapy in clinical practice without adequate studies to explore the correlation between this target concentration and treatment outcome in this particular patient population. Until now, all relevant studies were designed to test if the dosing strategies would achieve the target C_{pre-HD} of 15–20 mg/L in patients who were on intermittent HD[12, 14]. However, it has not been demonstrated whether the specific target C_{pre-HD} can be translated into good clinical outcomes.

文章的意義和重要性

According to the results of our study, the success and failure groups did not have significant differences in the mean C_{pre-HD} as well as the proportion of patients with the $C_{pre-HD} > 15$ mg/L. However, after taking MIC into consideration, C_{pre-HD}/MIC was significantly higher in the success group than that in failure group. Moreover, the ROC curve analysis suggested C_{pre-HD}/MIC$\geqq$18.6 as an outcome predictor for treating MRSA bacteremia. Our data were also compatible with previous recommendations that the target level of vancomycin C_{pre-HD} should be 15–20 mg/L for a MIC of 1 mg/L[9]. As for the MIC distribution, around 70% of MRSA had vancomycin MIC value of 1 mg/L and pathogens with high MIC value (>1.5 mg/L) were almost distributed in treatment failure group, which was compatible with previous studies that high MIC level was a predict factor for poor treatment outcome.[19] However, it is difficult to distinguish to what degree is the failure caused by not attaining the PK/PD target and to what degree the higher MIC caused failure. Therefore, we excluded patients who suffered from pathogens with high MIC value (>1.5 mg/L), and the C_{pre-HD}/MIC was still significantly higher in treatment success group than that in failure group (24.07 vs. 16.92, p = 0.04). This result demonstrated that attaining the optimal C_{pre-HD}/MIC was important for treatment outcome of MRSA bacteremia in this population. Because vancomycin MIC crept in MRSA, which had high percentage of vancomycin MIC of 1 mg/L, and nephrotoxicity is generally not an issue in patients receiving HD, the aggressive vancomycin dosing strategy to achieve $C_{pre-HD}\geqq$18.6 mg/L should be adopted before confirming MIC data[20].

解讀結果

Compared with a similarly designed study of vancomycin treatment in non-dialysis patients with MRSA bacteremia, the treatment success rate in this study was much lower (36% vs. 67.5%) despite of similar Charlson Comorbidity Index[4]. Two factors may explain the difference. First, the immune function is depressed in patients with renal failure. Functional abnormalities of monocytes, lymphocytes, neutrophils, and dendritic cells are directly linked with infection risk and treatment failure in this patient population.[8] Second, the formation of bacterial biofilm in dialysis patients may contribute to the high treatment failure rate. *Staphylococcus aureus* is the most common gram-positive organism involving in biofilm infection in dialysis patients [21, 22]. Some studies revealed that dialysis-related biofilm infections are difficult to eradicate as they developed antibiotic resistance[23–25]. Vancomycin has poor penetration into biofilm compared with daptomycin, and it is reasonable that the patients responded to daptomycin treatment in this study after vancomycin treatment failure.[26] Further studies are necessary to determine if daptomycin has better treatment effect than vancomycin in dialysis patients.

Based on our vancomycin dosing protocol for patients receiving HD three times per week, the proportion of $C_{pre-HD} \geqq 18.6$ mg/L was only 21%, which may have contributed to the relatively high rate of treatment failure. One possible cause for this low proportion of therapeutic C_{pre-HD} was that the loading dose used in the present study (<20 mg/kg) was too low. Vandecasteele et al. showed that a fixed loading dose of 20 mg/kg led to $C_{pre-HD} \geq 15$ mg/L in only one-half of patients[9], supporting that a higher loading dose should be applied in order to achieve the optimal therapeutic C_{pre-HD}.

和之前的文獻作比較，甚麼原因造成結果不同
未來的研究方向

Discussion

There are several limitations of our study. First, the sample size was quite small in this study because of the low MRSA prevalence rate and MIC report has been available since 2013 in our institution. Further large prospective study is needed to confirm the treatment target provided by this study. Second, we only enrolled patients undergoing HD; this result may not apply to patients receiving other renal replacement therapy, such as peritoneal dialysis. Third, this was a retrospective study, and thus was not controlled for some confounding factors. Finally, overweight and obese patients were not represented in this study. Therefore, the result may not apply to this special population.

研究限制

Conclusion

- 強而有力的總結

- 勿過度推論

  - Targeting to achieve a Cpre-HD/MIC of $\geqq$ 18.6 **(may vs. could)** improve the treatment outcomes in renal failure patients who are on intermittent HD.

Conclusions

We showed that $C_{\text{pre-HD}}$/MIC was associated with the outcome of vancomycin treatment in dialysis patients with MRSA bacteremia. Targeting to achieve a $C_{\text{pre-HD}}$/MIC of $\geqq$ 18.6 may improve the treatment outcomes in renal failure patients who are on intermittent HD.

Reference

- 注意投稿期刊規定
- 絕對不要用上標標示reference
  - 你會厭世，然後放棄

Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) is a common pathogen which

References

1. Centers for Disease C, Prevention. Invasive methicillin-resistant Staphylococcus aureus infections among dialysis patients—United States, 2005. MMWR Morb Mortal Wkly Rep. 2007; 56(9):197–9. PMID: 17347644.

2. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011; 52(3):e18–55. https://doi.org/10.1093/cid/ciq146 PMID: 21208910.

3. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet. 2004; 43(13):925–42. PMID: 15509186.

mycin AUC_{24}/MIC or C_{trough} and treatment outcome, few examined renal failure patients who received renal replacement therapy such as hemodialysis (HD)[3, 4, 6, 7]. The immune

Reference

- 注意投稿期刊規定

- 絕對不要用上標標示reference

  － 你會厭世，然後放棄

Introduction

The timely initiation of appropriate antibiotic therapy is crucial for

References

1 Zhang D, Micek ST, Kollef MH. Time to appropriate antibiotic therapy is an independent determinant of postinfection ICU and hospital lengths of stay in patients with sepsis. *Crit Care Med* 2015; **43**: 2133–40.

2 Falcone M, Bassetti M, Tiseo G *et al.* Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing *Klebsiella pneumoniae. Crit Care* 2020; **24**: 29.

3 Magill SS, Edwards JR, Beldavs ZG *et al.* Prevalence of antimicrobial use in US acute care hospitals, May-September 2011. *JAMA* 2014; **312**: 1438–46.

therapy has been reported to be 16.5%–37.3% and associated

Reference

- 注意投稿期刊規定
- 絕對不要用上標標示reference
  - 你會厭世，然後放棄
- 務必善用書目管理軟體
  - Endnote
  - Zotero
  - Mendeley

Abstract

- 最後寫，總結你的文章
- 寫摘要前請先選好你的目標期刊及研討會，格式及字數請參照相關規定
- 一般摘要內容
  - 簡單背景描述、研究目的，主要使用方法，重要結果及結論
- 縮寫: 很長的字詞第一次出現時給予定義，之後可使用縮寫。部分期刊有規定特定縮寫第一次不需解釋

Abstract

Background

Vancomycin is a standard treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, and its efficacy is closely linked to the recommended serum trough concentration of 15–20 mg/L. However, it is unknown how the pre-dialysis trough serum concentration (C_{pre-HD}) correlates with MRSA eradication in renal failure patients undergoing intermittent hemodialysis (HD).

Objective

To evaluate the relationship between C_{pre-HD} and the treatment outcomes in this population.

Materials and methods

A retrospective study was conducted to enroll renal failure patients undergoing HD who had received vancomycin treatment for MRSA bacteremia during January 2013 to June 2016. Treatment failure was defined as persistent bacteremia after ≥ 7 days of vancomycin therapy or recurrent MRSA infection within 30 days. Patient characteristics, vancomycin dosing regimen, C_{pre-HD}, vancomycin minimum inhibitory concentration (MIC), and subsequent culture data were reviewed. The receiver operating characteristic (ROC) curve was used to find the optimal cut-off point of C_{pre-HD}.

Results

42 patients were enrolled and 64% had treatment failure. Although there were no significant differences in demographics or C_{pre-HD} between the two groups, C_{pre-HD}/MIC was significantly higher in the success group than that in the failure group (22.80±10.90 vs. 14.94 ±6.11, $p = 0.019$). The area under the ROC curve was 0.74, while the sensitivity, specificity, positive predictive value, and negative predictive value were 67%, 78%, 62.5%, and 81%, respectively, at the optimal C_{pre-HD}/MIC of $\geqq 18.6$.

Conclusions

C_{pre-HD}/MIC was associated with vancomycin treatment outcome in MRSA bacteremia, and targeting to achieve a C_{pre-HD}/MIC of $\geqq 18.6$ may improve treatment outcomes in renal failure patients who are on intermittent HD.

Cover letter

- 告訴editor為什麼你的文章重要，內容適合這個期刊，讓editor一眼就愛上，馬上送出去審
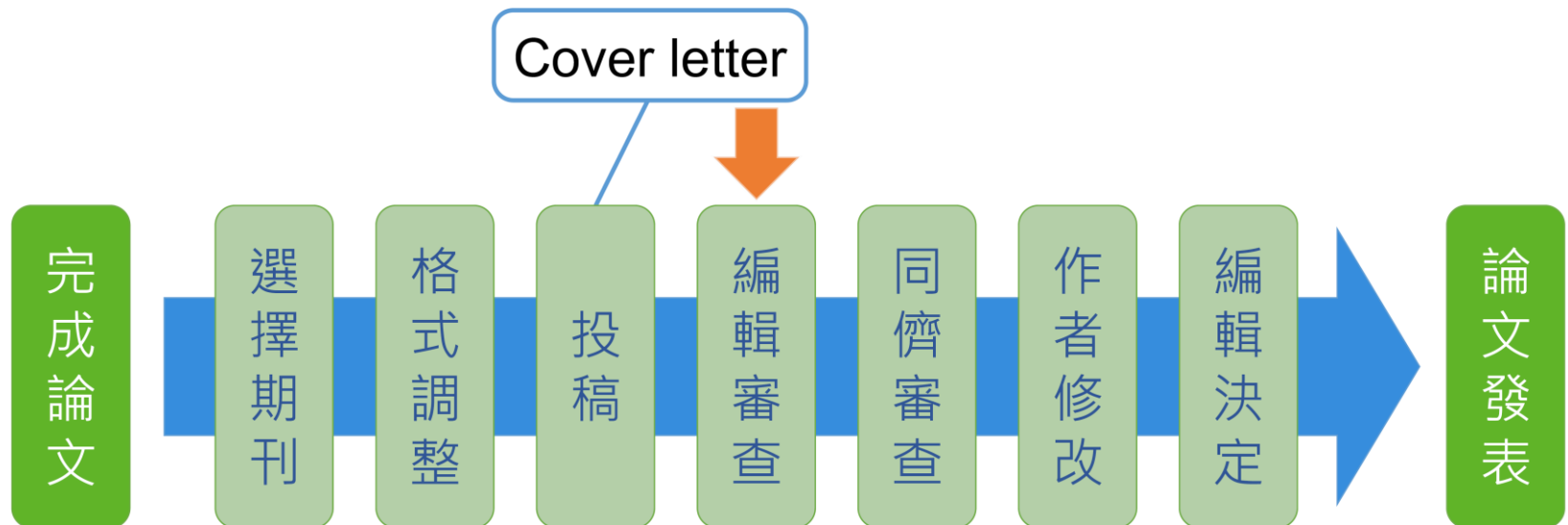
4. SAMPLE COVER LETTER

My Name
University of Research
804 Research Drive
Los Angeles, CA, USA 90210

310-555-1234
m.name@researchu.edu

Dr. John Editorian
Editor-in-Chief
Journal of Science

June 15, 2016

Dear Dr. Editorian:

I am pleased to submit an original research article entitled "Neofunctionalization of polymerase rho in Ustilago maydis" by Albert Postdoc and My Name for consideration for publication in the Journal of Science. We previously uncovered a role for polymerase rho in DNA repair in U. maydis [citation], and this manuscript builds on our prior study to determine the evolution of this unique enzyme.

In this manuscript, we show that polymerase rho... **[list a few important results]**.

We believe that this manuscript is appropriate for publication by the Journal of Science because it... **[specific link to the journal's aims & scope]**. Our manuscript creates a paradigm for future studies of the evolution of essential enzymes in yeast.

This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose, but we do respectfully request that Dr. Glen Meanie not review our manuscript. If you feel that the manuscript is appropriate for your journal, we suggest the following reviewers:
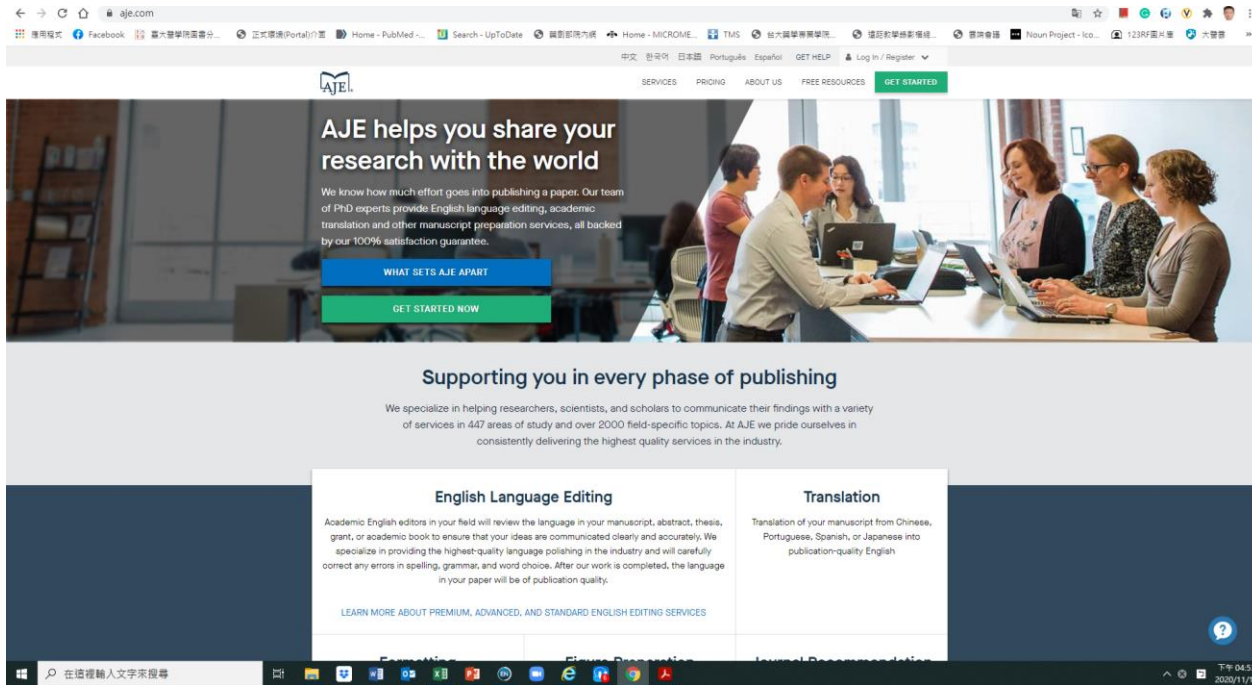
[list reviewers and contact information, if requested by the journal]

Thank you for your consideration!

Sincerely,

My Name, PhD
Professor, Department of Evolutionary Mycology
University of Research

Reference

WWW.AJE.COM

Take home message

Take home message

- Title – 一看就懂
- Abstract – 最後寫
- Introduction – 為什麼要作這個研究
- Material and methods – 讓別人可以重現
- Results – 忠實呈現結果
- Discussion – 解讀結果、和過去比較、提出限制
- Conclusions – 勿過度解讀
- Reference – 善用軟體

連絡資訊: r93451011@gmail.com