實證醫學

Evidence-Based Medicine

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Evidence-Based Medicine

- Definition: Use of current best evidence in making decisions about the care of individual patients.
 - **EBM** is the integration of best research evidence with clinical expertise and patients' unique biology, values and circumstances.

Pt

Ev

(Evidence-based Practice)

The Evidence Pyramid



Meta lalysis

Hierarchy of evidence: arranges study designs by their susceptibility to bias.

In vitro (test tube) research

Decision Making in Health Care

- What you learned during your professional training
- Browse journals
- Textbooks
- Ask colleagues

- Searching bibliographic databases
- Clinical practice guideline (CPG)
- "Do no harm"
- Evidence-based journal abstracts



Systematic review

Meta-analysis (Forest plot)

學習目標

- Five steps in practicing EBM
 - Formulate clinical question
 - Search database
 - Cochrane database, DARE, ACP journal club
 - UpToDate
 - PubMed clinical queries etc.
 - Level of evidence (I~V)
- Calculate NNT, NNH
 - number needed to treat (NNT=1/ARR)
 - number needed to harm (NNH=1/ARI)
 - Forest plot (meta-analysis)
- Practice
 - 主動積極 自我學習 Attitude and behavior change

實證醫學的五大進行步驟 Five Steps to Practice EBM

1. Formulate an answerable question.

由個案的臨床資料形成可回答的臨床問題

2. Track down the best evidence.

尋找最佳的實證〔各種文獻及資料庫,包括發表及未發表的資料〕

3. Critically appraise the evidence for validity, impact, and applicability.

評估各種醫學報告的可信度、臨床重要性,以及可應用性

- 4. Integrate with our clinical expertise and patient values. 整合並應用於實際患者的治療決策〔臨床應用〕
- 5. Evaluate our effectiveness and efficacy. 效果評估

1. Asking Answerable Clinical Questions

Well-built Clinical Question

- "Background" question
 - Ask general knowledge about a disorder
 - Have two essential components:
 - A question root (who, what, why, when...) with a verb
 - A disorder, or an aspect of a disorder
- "Foreground" question
 - Ask for specific knowledge about managing patients with a disorder
 - Have four (or three) essential components (PICO):
 - 1. Patient and/or problem: Who is the patient or what is the problem being addressed?
 - 2. Intervention: What is the intervention (treatment)?
 - 3. Comparison intervention: What are the alternatives?
 - 4. Outcomes: What are the outcomes?

Asking Answerable Clinical Question

Patient/Problem	Insulin-dependent diabetics
Intervention	Intensive insulin regimen
Comparison	Regular insulin regimen
Outcomes	Retinopathy
	Symptomatic hypoglycemia

2. Searching The Best Evidence

尋找最佳實證資料

- 直接使用實證醫學資料庫 (secondary journals or databases) ~ ACP journal club, Cochrane.
- 或是找研究論文資料庫 (primary journals or databases) ~ 如 Medline, NEJM, Lancet...
- 搜尋與病人問題相同且證據等級 (level of evidence) 較高之文獻,再謹慎評讀與評估其在此問題的適用性

實證醫學主要的四個資料庫

- 1. ACP Journal Club: 含括「ACP Journal Club」(American College of Physicians, 美國內科醫師學會出版)與「Evidence-Based Medicine」(ACP 與 British Medical Journal Group合作出版)兩種出版品,每月至少過濾50種以上之核心期刊,搜尋最佳之原始與評論性文章,結構化整理摘要出其中重要實證所得。
- 2. DARE: Database of Abstracts of Reviews of Effectiveness 收錄評論性文章的全文型資料庫,由 National Health Services' Centre for Reviews and Dissemination (NHS CRD)組織出版,此一組織針對部份經過評估、挑選有學術價值的醫學期刊中選出系統性評論的文章,並將之集合而成 DARE。
- 3. CDSR: Cochrane Database of Systematic Reviews 為「Cochrane 合作研究機構」(Cochrane Collaboration)所出版, 其為一個人與機構共同組成之國際性網路組織,有系統的研究上百種期刊文獻,專門從事有系統的評論儲備、維護和傳遞影響醫療保健相關之業務主題性評論。
- 4. CCTR: Cochrane Central Register of Controlled Trials 超過 400,000筆有關健康保健的控制實驗樣品參考型書目資料,內容包括 RCT〈Randomized Controlled Trials〉及 CCT〈Clinical Controlled Trials〉。由Cochrane groups 及其單位組織將 Medline 及 EMBASE 檢索出來的隨機樣品文獻登記集中而成。

Source of Evidence

- 1. Cochrane library, ACP, DARE
- 2. UpToDate, MD consult
- 3. PubMed, Medline
 - Clinical queries
- Clinical evidence
- Best evidence
- Guidelines Clearinghouse
- ... (Evidence is never enough)

Text PubMed

Overheev

Corners

Overheev

Overheev

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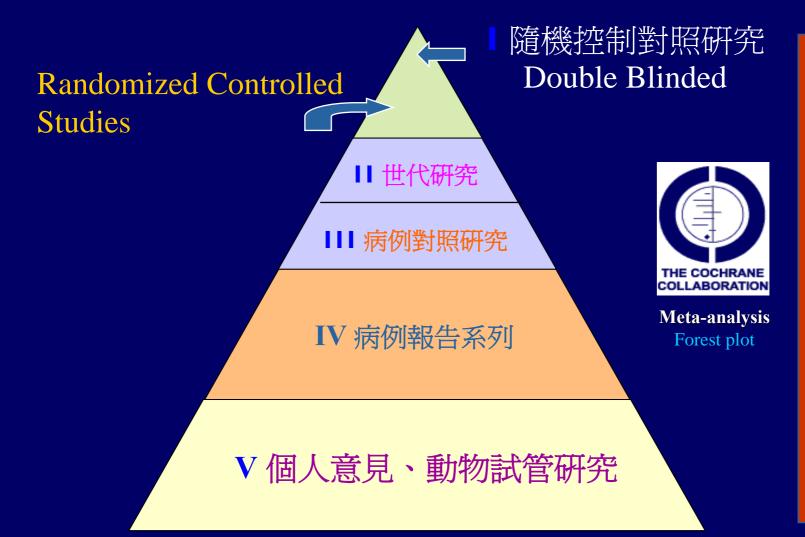
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E-Utilites

PubMed Services
Journals Database

Most Databas

Free: http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html

Level of Evidence: I~V



研究設計與證據強度(Bias, Robust)

Grade of Recommendation	Level of Evidence	Therapy
[A]	1a	Systemic review of RCTs
	1b	Single RCT
	1c	'All-or-none'
[B]	2a	Systemic review of cohort studies
Evidence-Based Medicine: How to Practice	2b	Cohort study or poor RCT
and Teach EBM. 2nd ed. David L. Sackett, Sharon E. Straus, W. Scott Richardson,	2c	'Outcomes' research
William Rosenberg, R. Brian Haynes. Churchill Levingstone. 2000, p173-177	3a	Systemic review of case- control studies
	3b	Case-control study
[C]	4	Case series
[D]	5	Expert opinion, physiology, bench research

3. Critically Appraising the Evidence (VIP)

- Critically appraising the evidence for its (VIP)
 - Validity (closeness to the truth)
 - 1. Was the assignment of patients to treatment randomized?
 - 2. Was follow-up of patients sufficiently long and complete? (> 80%)
 - 3. Were all patients analyzed in the groups to which they were randomized? (ITT, Intension To Treat analysis)
 - 4. Were patients and clinicians kept blind to treatment?
 - 5. Were groups treated equally, apart from the experimental therapy?
 - 6. Were the groups similar at the start of the trial?
 - Validity: selection bias, information bias, confounding
 - Reliability of measurement: intraobserver (similarity over time), interobserver, internal consistency
 SD, variance, 95% CI (confidence interval), p value
 - mpact (size of the effect):
 - NNT (number needed to treat) = 1/ARR (absolute risk reduction)
 - NNH (number needed to harm) = 1/ARI (absolute risk increase)
 - Applicability (usefulness in our clinical practice)
 - Integrating the evidence with our clinical expertise and patients' values and preferences.

From RR to ARR and NNT

Measures of the effects of treatment: RRR, ARR

	Event rate = pro disability by 33		Relative risk reduction (RRR = ICER - EERI/CER)	Absolute risk reduction (ARR = ICER - EERI)	Number needed to treat (NNT = 1/ARR)	
	Control event rate (on placebo) (CER)	Experimental event rate (on interferon) (EER)	RRR	ARR	NNT	
In the actual trial Lancet 1998; 352: 1491-7	50%	39%	(50% - 39%)/50% = 22%	50% - 39% = 11%	1/11% = 9	
In the hypothetical trivial case	0.00050%	0.00039%	(0.00050% - 0.00039%)/ 0.00050% = 22%!	0.00050% - 0.00039% = 0.00011%	1/0.00011% = 909 090	

RRR can not discriminate huge treatment effects from small ones!

Asking Answerable Clinical Question

Patient/Problem	Insulin-dependent diabetics
Intervention	Intensive insulin regimen
Comparison	Regular insulin regimen
Outcomes	Retinopathy
	Symptomatic hypoglycemia

Treatment Effects

- Occurrence of diabetic retinopathy at 5 years among insulindependent diabetic in the DCCT trial
- Usual insulin regimen (CER: control event rate): 38%
- Intensive insulin regimen (EER: experimental event rate): 13%

Risk Reduction (calculation): NNT

- Absolute risk reduction (ARR)
 - = | CER-EER | = 38%-13% = 25%
- Relative risk reduction (RRR)
 - = | CER-EER | /CER = 25%/38% =66%
- Number needed to treat (NNT)
 - = 1/ARR = 1/25% = 4 patients
 - NNT: The number of patients that need to be treated to prevent one bad outcome or get one good outcome.
 - 增加一位病患得到某種處置好處所需的治療病人數=1/ARR,即 與對照組療法相比而言,使一位病人達到實驗組治療之有利結果(或預防產生不利結果)所需治療的病人數目。(越少越好)

Harm

- The proportion of patients with at least one episode of symptomatic hypoglycemia
- Usual insulin regimen (CER: control event rate): 23%
- Intensive insulin regimen (EER: experimental event rate): 57%

Risk Increase (calculation): NNH

- Absolute risk increase (ARI) = EER CER = 57% 23% = 34%
- Relative risk increase (RRI) = EER-CER/CER = 57% 23%/23% = 148%
- Number needed to harm (NNH) = 1/ARI = 1/0.34 = 3 patients (取整數)
 - NNH: The number of patients that need to be treated to cause one bad outcome (being harmed).
 - 增加一位受試者罹患某種醫源性傷害的治療病人數:即對多少病人進行 實驗組治療〔與對照組療法做比較〕會有多一個病人產生不良副作用。 (數目越大越好)

Critically Appraising the Evidence

評估文章的可信度 (Validity)和實用性 (注意研究選入病人的條件)

- 病人的分組是隨機分派的嗎?(random allocation)
- · 分派的方法是否保密?(concealment of allocation)
- 追蹤是否完整?(follow-up duration)(>80%)
- · 治療方法對病患、醫護人員、研究者是否blinded?
- 分析時是否利用intention-to-treat analysis?
- 除了研究治療項目以外,其他的治療在各組間是否相同?
- · 兩組在治療開始時的baseline是否相似?
- 在閱讀每一篇文章時,要注意是否符合這些基本原則,如果沒有,是 爲什麼沒有,對於結果有沒有影響?另外還要考慮文章的結果對病人 實際上的意義爲何?重不重要 (impact: size of effect, NNT, NNH)?
- 當有了一個可信的結果,接下來要評估這個結果的臨床意義,文章常以RRR (Relative risk reduction)來表示療效,但以 NNT (Number Needed to Treat),及 NNH (Number needed to harm)來表達更爲直接。

臨床問題類型

- 危害或致病因子探討 (Risk)
 - Cohort study (Relative Risk)
 - Case-control study (Odds Ratio)
- 🏓 診斷 (Diagnosis)
 - Sensitivity, specificity
 - Predictive value (PPV, NPV, Likelihood Ratio)
- 治療 (Therapy)
 - Clinical trial (Randomized Controlled Trial)
- 預後 (Prognosis)
 - Prediction model (Survival analysis)

統計數字會說話

評估時以具體的數字呈現結果

- 敏感度 (sensitivity)、特異度 (specificity)、陽性預測値 (Positive predictive value)、陰性預測値 (Negative predictive value)、概似比 (likelihood ratio)、檢測前機率 (pre-test probability)、檢測後機率 (post-test probability)
- 相對危險 (Relative risk)、勝算 (Odds)、勝算比 (Odds ratio) 、 信賴區間(confidence interval)
- ARR (Absolute risk reduction) = EER (Experimental Event Rate) CER (Control Event Rate) 、相對危險度減少百分比 (relative risk reduction, RRR) 、 Number needed to treat, NNT=1/ARR (增加一位病患得到某種處置好處所需的治療病人數)
- 絕對危險度增加百分比 (absolute risk increase, ARI) = EER (Experimental Event Rate) CER (Control Event Rate)、 Number needed to harm, NNH=1/ARI (增加一位受試者罹患某種醫源性傷害的治療病人數)

Calculation of OR/RR

Treatment	Event (Disease)	
	Positive	Negative
Exposed (experimental)	A = 1	B = 29
Not exposed (control)	C = 9	D = 21

EER = a/a + b = 0.033

(Cohort study, Clinical trial)

 $\overline{\text{CER (control event rate)}} = c/c+d = 0.30$

Relative Risk = **EER/CER** = (a/a+b)/(c/c+d) = 0.11

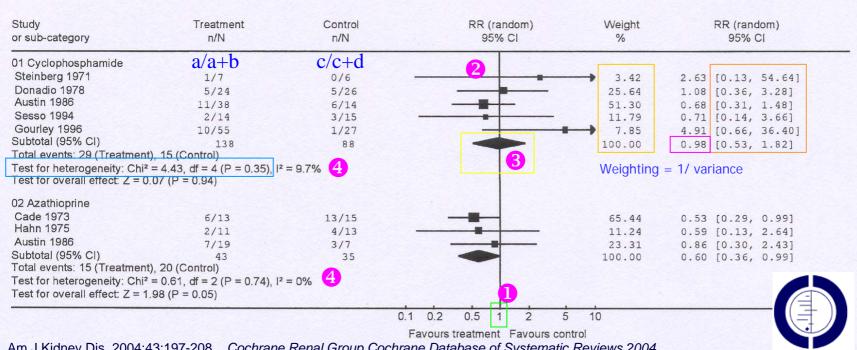
Experimental event Odds = a/b = 0.034 (Case control study)

Control event Odds = c/d = 0.43

Relative Odds = Odds Ratio = (a/b)/(c/d) = ad /bc = 0.08

^{*} Odds: a ratio of event to nonevent, Probability = event / (event+nonevent)

Forest plot (Meta-analysis)



Am J Kidney Dis. 2004:43:197-208. Cochrane Renal Group Cochrane Database of Systematic Reviews 2004.

- Fig 2. Effect of cyclophosphamide and azathioprine plus steroids versus steroids alone on overall mortality in patients with DPLN. There is no significant reduction in risk for mortality with cyclophosphamide, whereas azathioprine significantly reduces the risk. Heterogeneity across these trials is not significant.
- 1 This is a **forest plot**, with a **vertical line** at **1.0** representing equivalence in risk for an outcome with experimental and control treatment (null hypothesis). Values of RR less than 1 indicate a reduction in risk for the outcome with the experimental treatment. Conversely, values of RR more than 1 indicate an increase in risk.
- 2 The RR for each outcome and its 95% CI are indicated by a solid square and a line. The 95% CIs are a measure of variability in the precision of the RR estimate and its statistical significance. The size of the solid square represents the contribution (weight) of the trial to the analysis. 3 Diamond-shaped symbols represent the summary estimator of overall effect pooling the weighted effect of individual RCTs.
- 4 Heterogeneity ('non-combinability') of treatment effects between studies was investigated by visual examination of graphic meta-analysis plots and from the Cochran Q (heterogeneity chi-square) and I² statistic.

Diagnosis LR: likelihood

Diagnostic test	Disease (IDA)			
(ferritin)	Present		Absent	
Positive (陽性)	731	a	b	270
Negative (陰性)	78	С	d	1500

PPV

NPV

Sensitivity = a/a+c = 731/809 = 90%

SnNout, SpPin

Specificity= d/b+d = 1500/1770 = 85%

Positive predictive value (PPV) = a/a+b = 731/1001 = 73%

Negative predictive value (NPV) = d/c+d = 1500/1578 = 95%

*Note: 診斷試驗的預測值 (predictive value) 受疾病盛行率 (prevalence) 影響。

Positive predictive value (PPV) = Sen . P / [Sen . P + (1-Sp) . (1-P)] (Bayes's theorem)

P=0.5, PPV=0.8x0.5 / [0.8x0.5+0.2x0.5] = 0.8 = 80.0%

P = 0.05, $PPV = 0.8 \times 0.05 / [0.8 \times 0.05 + 0.2 \times 0.05] = 17.4\%$

P = 0.005, PPV = 0.2%

同一診斷工具,在不同盛行率情況下,其 Predictive value 結果不同。~ LR 概似比

Specificity 高,但運用在盛行率低的族群時,大部分陽性結果是假陽性。 Sensitivity 高,但運用在盛行率高的族群時,大部分陰性結果是假陰性。

a. LR: likelihood ratio = post-test odds / pre-test odds

b. Pre-test probability (prevalence) = a+c/a+b+c+d= 31%

c. Pre-test odds = prevalence/(1-prevalence) = 31%/69% = 0.45

Diagnosis LR: likelihood ratio (multi-level)

Diagnostic test	Disease (IDA)			
(ferritin)	Present		Absent	
Positive (陽性)	731	a	b	270
Negative (陰性)	78	С	d	1500

PPV

NPV

1. Sensitivity = a/a+c = 731/809 = 90%Specificity= d/b+d = 1500/1770 = 85%

SnNout, SpPin

- 2. Positive predictive value (PPV) = a/a+b = 731/1001 = 73%Negative predictive value (NPV) = d/c+d = 1500/1578 = 95%
- 3. LR+ for a positive result = sens/(1-spec) = a/(a+c) / b/(b+d) = 90%/15% = 6陽性概似比 LR+: 有病者與無病健康者, 檢驗呈陽性的機率比 = 敏感度 / (1-特異度)

LR- for a negative result = (1-sens)/spec = c/(a+c) / d /(b+d) = 10%/85% = 0.12

Pre-test probability (prevalence)= a+c/a+b+c+d= 31%

Pre-test odds = prevalence/(1-prevalence) = 31%/69% = 0.45

Post-test odds = Pre-test odds × Likelihood Ratio

odds & probability 換算: probability = odds / (odds + 1)

4. 實證醫學的五大進行步驟 Five Steps to Practice EBM

- Step 1. Converting the need for information (about prevention, diagnosis, prognosis, therapy, causation, etc.) into an answerable question. (PICO)
- Step 2. Searching the best evidence with which to answer that question.
- Step 3. Critically appraising the evidence for its validity (closeness to the truth), impact (size of the effect), and applicability (usefulness in our clinical practice). (VIP)
- Step 4. Integrating the evidence with our clinical expertise and patients' unique biology, values and circumstances.
- Step 5. Evaluating our effectiveness and efficiency in executing steps 1-4 and seeking ways to improve them both for next time.

Two Fundamental Principles of EBM

- EBM posits a hierarchy of evidence to guide clinical decision making.
- Evidence alone is never sufficient to make a clinical decision.
 - Trade the benefits and risks
 - Costs
 - Inconvenience
 - Consider the patient's value

資料數據分類(統計數字)

- ●類別型 (Categorical data)
 - 名目變項 (Nominal variable): 性別、人種
 - 次序變項 (Ordinal variable): 教育、喜好程度
- 數値型 (Numerical data)
 - ·離散型 (Discrete): (整數值),家中小孩人數
 - 連續型 (Continuous): (可插入小數),身高

統計檢定: Z test 檢定, t test 檢定, 變異數分析 (ANOVA), 相關分析 (Correlation analysis), 回歸分析 (Regression analysis), 複回歸分析 (Multiple regression analysis), 無母數分析 (Nonparametric analysis, X²)

統計方法的選擇 Selecting a Statistical Test

	名義	數值
名義	大樣本 卡方檢定 X² test 小樣本 Fisher's exact test 相關強度 odds ratio (OR)	兩組平均値比較 - t test 三組平均値比較 - ANOVA
數值	X	相關分析 correlation coefficient (r) 線性迴歸 y= a+b ₁ x ₁ +b ₂ x ₂

Z test 檢定, t test 檢定, 變異數分析 (ANOVA, F檢定), 相關分析 (Correlation analysis), 迴歸分析 (Simple or multiple regression analysis: number of x axis), 無母數分析 (Nonparametric analysis, 卡方X²)

Selecting a Statistical Test

	Type of Data				
Goal	Measurement (from Gaussian Population) 連續變項且爲常態分佈	Rank, Score, or Measurement (from Non- Gaussian Population)	Binomial 二項式變數 (Dichotomous) (Two Possible Outcomes)		
Describe one group	Mean, SD	Median (Q ₂), interquartile range (Q ₁ -Q ₃)	Proportion (%)		
Compare one group to a hypothetical value	One-sample t test	Wilcoxon test	Chi-square or Binomial test		
Compare two unpaired groups	Two-sample t test (unpaired t test)	Mann-Whitney test/ Wilcoxon rank-sum test	Fisher's test (chi-square for large samples)		
Compare two paired groups	Paired t test	Wilcoxon signed-rank test	McNemar's test		
Compare three or more unmatched groups (≥3)	One-way ANOVA	Kruskal-Wallis test	Chi-square test		
Association between two variables	Pearson correlation	Spearman correlation	Contingency coefficients		
Predict value from another measured variable	Simple linear regression	Nonparametric regression	Simple logistic regression		
Predict value from several measured or binomial variables	Multiple linear regression		Multiple logistic regression		

Variable: 變項、變數

(區分 y 與 x 的資料類型是屬於:數值型或類別型)

Multiple Regression Analysis

 $y = \alpha + \beta_1 x_1 + \beta_2 x_2 + ... + \beta_1 x_1$

y: SBP (數值) or 血壓高或正常 (類別) ★:Age Sex Race BH BW CH TG

Dependent variable 依變數
Response variable 應變數
Outcome variable 結果變數
Predicted

(y: 因自變數x改變而發生改變的 結果變數)

Independent variables 自變數
Explanatory variables 解釋變數
Covariates (in ANCOVA) 共變數
Predictor variables

Factor 因子 (in ANOVA)~ One way



九十三年度 畢業後一般醫學訓練計劃 一般醫學内科93年9~11月 EBM 問題分析單集

財團法人長庚紀念醫院 編ED 醫學教育委員會 中華民國九十三年十一月

林口長庚醫院 EBM - PBL 臨床問題分析表單

日期:94/01/10	期:94/01/10 Case Chart No:20652811 報告者:張光正						
科別:chest 1	職級:■Resident □Intern □Clerk □V.S. 成日:94/01/06						
問題敘述 (Pr	oblem	descript	tion):				
n adult patien	ts with	acute a	sthma treated in	the emergency sett	ing, does the addition		
				ists have an addition			
effect?		1-5	to [eetin]2 ugo.i	isto navo un udunto.	nai oronomanom		
搜尋關鍵字 (Kev w	vord):					
aminophylline	120	250	ute asthma				
шшорпушше	,ircan	nem, ac	ate astima				
資料來源「R	eferen	ce] ~ A	CP Journal Club	and Best Evidence	Convright 2001		
				Society of Internal			
					viedicine		
Volume 134(3)		10. 1100	ay/June 2001	p 97			
文獻等級: _I	_ (L	evel of e	vidence ::				
主要內容 (M	ain res	ults):					
15 trials met	the sel	ection c	riteria. Treatmen	t groups did not dif	fer for airflow		
					igher values of PEF		
				group differences we			
				at baseline nor the			
			ohylline. Patients	s in the aminophylli	ne group reported		
nigher rates of	palpit	ations					
Outcomes	Am	Placebo	Weighted mean difference (95% C	1)			
PEF (L/min, 12 h)	194	184	8.3 (21 to 37)				
PEF (L/mm, 24 h)	216	209	22.2 (-57 to 101)				
FEV ₁ (L, 12 h)	2.0	1.6	0.4 (-0.2 to 1.0)				
FEV ₁ (L, 24 h)	2.2	1.8	0.4 (-0.1 to 1.0)				
Arrhythmia/palpitations†	25%	10%	RRI (CI) 44% (4 to 29)	NNH (CI) 7 (4 to 24)			
Vomiting†	31%	9%	225% (112 to 368)	5 (3 to 10)			
Tremort	44%	35%	29% (7 to 67)	Not significant			
			RRR (CI)	NNT (CI)			
Hospitolized	21%	28%	35% (-1 to 51)	Not significant			
PH - peck expending flow Other of Infollowing time not provided.			, NNH, NNH, one (I colculated from dute 3+ ort	isle.			

In adult patients with acute asthma, the addition of intravenous aminophylline to [beta]2-agonists does not lead to additional bronchodilation, but some adverse effects were reported more frequently.

教師回覆:

可諮詢之人員或單位: 各主治醫師、實證種子講師

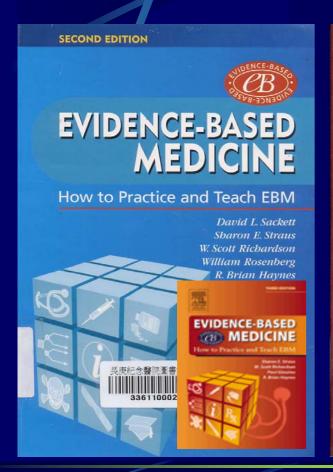
實證資料庫查詢網址: http://lnkwww.cgmh.org.tw/intr/intr2/ebmlink/index.htm

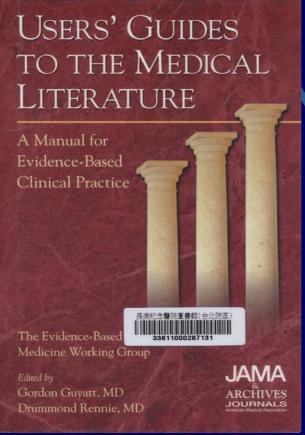
林口長庚醫院 實證醫學推廣架構

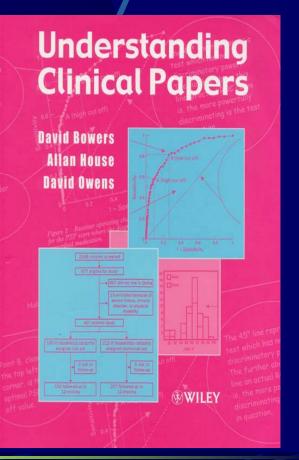
- 醫學生:醫學系及中醫系六年級實證醫學選修課程〔94.01~94.05〕
- 住院醫師:PGY1在內科一般醫學訓練時每週做一次EBM臨床病例討論 並請PGY1與臨床教師討論。每年6-9月做新進人員EBM Orientation.
- 並治醫師:94.01.22以各次專科總醫師為主要對象之實證醫學工作 坊,預計未來各科總醫師晉升為主治醫師前,必需通過實證醫學訓練 認證。92年4月起舉行EBM Grand Round,目前持續進行中.
- 全院性:每年舉行EBM introduction及EBM教學〔包括如何評讀論文,設計研究〕各一次。94.03.26舉辦全國性實證醫學研討會。
- 實證醫學中心每個月開會一次,討論實證醫學的核心知識;實證醫學中心在醫教會建有網頁做整體概念性介紹,並開放提供Power Point做線上學習,以具備實證醫學核心知識及方便網路資料搜尋。
- 實證醫學中心主治醫師成員:朱世明,歐良修,江東和,陳漢明,謝邦鑫,李宗料、陳敏煜,彭秀慧,張鴻,高振益,高國晉,田亞中,陳永昌,陳俊吉,黃兆山,楊宗翰,余光輝,簡竹君。實證醫學指導顧問:醫教會副主委方基存教授,婦產科張廷彰主任,長庚大學公衛科生統中心史麗珠博士,長庚大學醫務管理學系暨工管

系許光宏博士。

實證醫學參考書籍







進階學習

目前國外推動實證醫學著名的單位

- 加拿大McMaster University的HIRU(Health Information Research Unit)是Cochrane Collaboration的重鎭
 - http://hiru.mcmaster.ca/
- 英國Oxford University的 Centre for Evidence-Based Medicine
 - http://cemb.jr2.ox.ac.uk
- 美國American College of Physician (ACP),在 全球資訊網出版 ACP Journal Club Online
 - http://www.acpjc.org