Sliver-coated endotracheal for prevention of ventilator associated pneumonia in critically ill patients

(review)

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研究大綱

- 背 景
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- 方 法
- 結 果
- 結 論

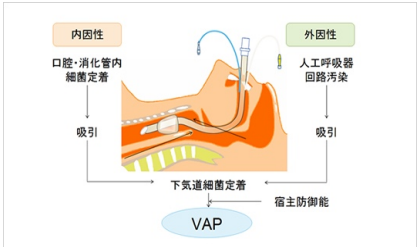
背 景

背 景

Ventilator Associated Pneumonia (VAP)

(NNIS 2004; Vincent 1995; Cook 1998a; Rello 2002a)

背 景



背 景

- In the ICU and hospital
- Hospital mortality
- Healthcare costs

(Safdar 2005)

背景

has been used both as a prophylactic agent and as a treatment for infectious and other diseases for many centuries.

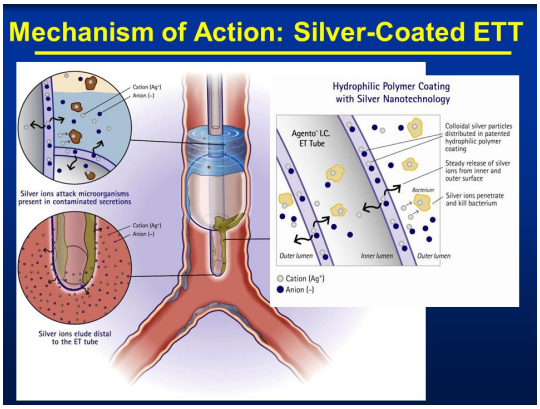
背景

Sliver-Coated ETTs contain silver atoms that are slowly released as silver cations.

背景

It is these silver ions that appear to have a strong antimicrobial effect.

- Bind to bacterial cell wall
- Bind to bacterial enzymes
- Bind to bacterial deoxyribonucleic acid (DNA)



目 地

目 的

Primary objective

Silver-coated ETT is effective in reducing the risk of VAP and hospital mortality in people who require mechanical ventilation for 24 hours or longer.

目 的

Secondary objective

Ascertain whether silver-coated ETTs are effective in reducing the following clinical outcomes:

1. Device-related events
2. Duration of intubation
3. Length of stay in ICU and hospital
4. Cost-effectiveness of silver-coated ETTs
5. Time to VAP onset

方 法

方 法

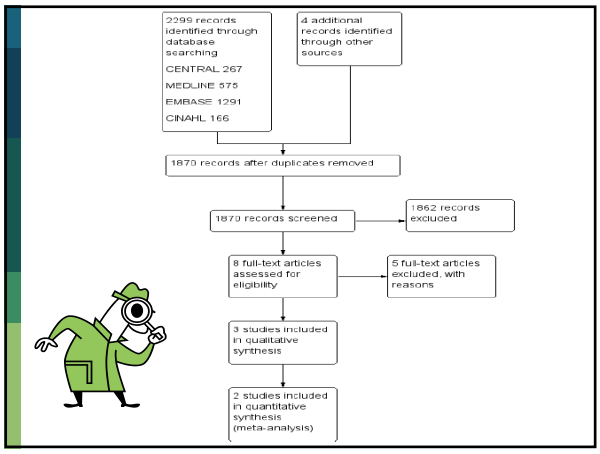
Cochrane Library

CINAHL Basic Searching Tutorial

EMBASE

MEDLINE

- http://apps.who.int/trialsearch/
- http://clinicaltrials.gov;
- www.controlled-trials.com;
- www.clinicaltrialsregister.eu.



方 法

Criteria for considering studies for this review

- **Types of studies**
- **Types of participants**
- **Types of interventions**
- **Types of outcome measures**

Types of studies

- Randomized controlled trials (RCTs)
- Quasi-randomized trials
- Clinical studies

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Types of participants

- Included:
  adult ICUs
  intubated and mechanically ventilated
  intubated for 24 hours or longer
- Excluded:
  under 16 years participants
  re-intubated

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Types of interventions

- Included:
  compared silver-coated ETTs or a combination of silver and any antimicrobial-coated ETTs.
  non-coated ETTs or with other antimicrobial(chlorhexidine)coated ETTs.
- Excluded:
  studies in which silver-coated ETTs were not evaluated in the intervention or control groups.

Types of outcome measures

Primary	Secondary
• Risk rate of VAP • hospital mortality	• Device-related events • Duration of intubation • Length of stay in ICU and hospital • Cost-effectiveness of silver-coated ETTs • Time to VAP onset

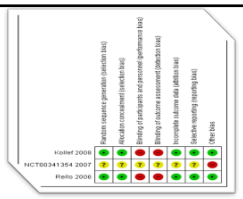
偏 誤(BIAS)

定義：

研究設計與執行過程，導致數據(data) 、結果(outcome)，朝向(toward)或偏離真實(against truth)的因子

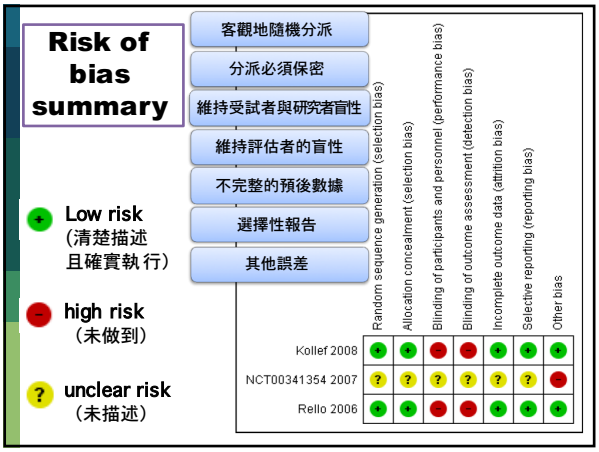
會使研究之內部效度 (internalvalidity)降低

偏 誤(BIAS)



使用考科藍誤差風險評估工具(Cochrane risk of bias tool)來評估研究品質

2名審查者(Tokmaji G,Zaat SAJ)獨立審閱納入研究之品質，所有的分歧通過討論和協商解決

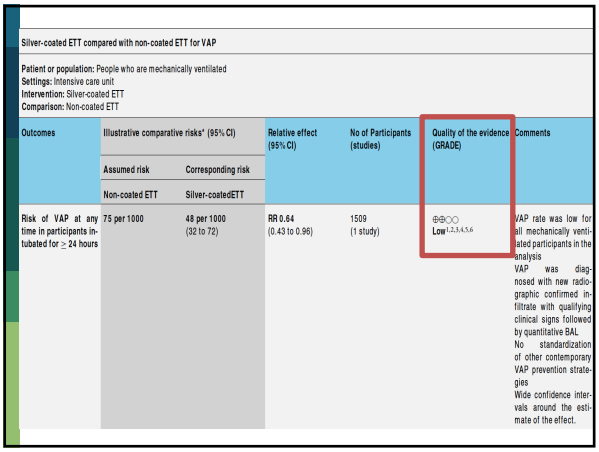


GRADE

是針對通過系統性文獻回顧的方式獲得的證據(evidence body) 所包含的研究結果進行分級，不是針對單個研究或單篇系統性文獻回顧進行分級

證據品質：**對於支持某項特定建議效果估計的信心**

臨床建議強度：指建議被實施後帶來的利益及風險



Silver-coated ETT compared with non-coated ETT for VAP

Patient or population: People who are mechanically ventilated
Settings: Intensive care unit
Intervention: Silver-coated ETT
Comparison: Non-coated ETT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Non-coated ETT	Corresponding risk Silver-coatedETT				
Risk of VAP at any time in participants intubated for ≥ 24 hours	75 per 1000	48 per 1000 (32 to 72)	RR 0.64 (0.43 to 0.96)	1509 (1 study)	⊕⊕◯◯ Low[1,2,3,4,5,6]	VAP rate was low for all mechanically ventilated participants in the analysis VAP was diagnosed with new radiographic confirmed infiltrate with qualifying clinical signs followed by quantitative BAL No standardization of other contemporary VAP prevention strategies Wide confidence intervals around the estimate of the effect.

GRADE 證據品質

表1. GRADE證據等級與定義

證據等級	定義
高（high）	未來的研究「不太可能」改變目前對效益的估計。
中（moderate）	未來的研究「可能」影響到我們目前對效益估計的信心，甚至可能改變此估計值。
低（low）	未來的研究「很可能」影響到我們目前對效益估計的信心，甚至可能改變此估計值。
非常低（very low）	這些效益估計都是非常不確定的。

GRADE 證據品質

對證據品質的判斷也始於研究設計:

隨機對照試驗：起始證據等級評為『高』
有五個降級因素
觀察性研究：起始證據等級評為『低』
有三個升級因素

★可能降低證據品質 (Downgrading) 的因素及其解釋	
偏差風險 (Risk of bias)	考科藍合作組織偏差風險評估工具(The Cochrane Collaboration’s tool for assessing risk of bias)評估的項目包括：隨機序列產生的方式(sequence generation)、分組隱匿(allocation concealment)、對受試者和研究人員及結果評估者實施盲法(blinding of participants, personnel and outcome assessors)、結果數據不完整(incomplete outcome data)及選擇性報告(selective outcome reporting)，以及其他未能分類的偏差(other bias)等。隨機序列產生的方式及分組隱匿用以評估是否產生選擇偏差(selection bias)、實施盲法用以評估是否產生表現性偏差(performance bias)、結果數據不完整則是評估是否出現失訪偏差(attrition bias)及報告偏差(reporting bias)，這些偏差的存在會影響文獻的品質(Higgins & Green, 2011)。未正確隨機分組、未進行分組隱匿、未實施盲法(特別是結果指標為主觀性指標、且其評估結果易受人為影響時)、研究失訪過多、未進行意向性分析、選擇性報告結果(尤其是僅報導觀測到有效結果的資料)、發現有療效後提前終止研究等，證據品質需降級。
不一致性 (Inconsistence)	在排除了合理的原因外，不同研究間仍然出現了大相逕庭的結果，可能意味著各種療法的療效確實存在差異。差異可能源於人群(如：藥物對重症病人族群的療效可能相對顯著)、介入措施(如：使用較高劑量的藥物，會使療效更顯著)或結果指標(如：隨時間推移、療效降低)。當結果存在不一致，而研究者未能意識到、並給出合理解釋時，證據品質需降級。
間接性 (Indirectness)	有兩類：一是欲比較兩種介入措施的療效時，沒有二者直接比較的隨機對照試驗，但可能存在均與同一安慰劑比較的隨機對照試驗，這樣的試驗可進行二者之間療效的間接比較，但提供的證據品質比直接比較的隨機對照試驗要低。第二類間接證據包括人群、介入措施、對照措施、預期結果等存在間接性。
不精確性 (Imprecision)	當研究納入的病人和觀察事件相對較少、而使得信賴區間較寬時，將降低其證據品質。
發表偏差 (Publication bias)	若研究者未能發表研究(通常是顯示介入措施無效的研究)時，證據品質亦會減弱。典型情況是當公開的證據僅局限於少數試驗，而這些試驗全部由廠商贊助，此時應懷疑存在發表偏差。

★可能增加證據品質 (Upgrading) 的因素及其解釋	
結果顯著 (Large effect size)	當方法學嚴謹的觀察性研究顯示療效顯著、或非常顯著，且結果一致時，將提高其證據品質。
干擾因素可能減少效果 (All plausible confounding would reduce a demonstrated effect)	當影響觀察性研究的誤差不是誇大，而是減小其效果時，可提高其證據品質。
證據顯示存在劑量－效應關係 (Dose-response gradient)	當介入的藥物劑量和引起的效應大小之間有明顯關聯時，可提高其證據品質。

GRADE 臨床建議強度

建議強度分級	具體描述
強 (1)	明確顯示介入措施利大於弊或弊大於利
弱 (2)	利弊不確定或無論品質高低的證據均顯示利弊相當

結 果

Kollef 2008

Methods	Mulitcentre, prospective, randomized, single-blind, controlled study
Participants	**Setting:** 54 centres throughout North America (Canada & USA). **Inclusion criteria:** Adults at least 18 years old eligible for enrolment if they were expected to require mechanical ventilation with an endotracheal tube for 24 hours or longer **Exclusion criteria:** Participation in another study that conflicted with the current study, bronchiectasis, severe or massive haemoptysis, cystic fibrosis, pregnancy, silver sensitivity, and endotracheal intubation for longer than 12 hours within the preceding 30 days **Participant numbers:** 2003 randomly assigned; 494 excluded (71 not intubated, 423 intubated < 24 h); 1932 all intubated; 1509 intubated ≥ 24 h analysed. 766 silver-coated ETT versus 743 non-coated ETT who were intubated for ≥ 24 h
Notes	No differences were noted between groups in APACHE II scores, use of enteral nutrition, presence of immunodeficiency, or other risk factors for VAP Chronic obstructive pulmonary disease was more common in the group receiving the non-coated tube (P value = 0.007) Cause of hospital mortality was not specified in this study VAP was diagnosed by clinical and radiographic parameters combined with culture-positive fluid obtained by BAL. Explicitly, new radiographic confirmed infiltrate with qualifying clinical signs were triggers for conducting quantitative BAL No standardization of prevention strategies at the clinical sites that participated in the study

Rello 2006

Methods	Mulitcentre, prospective, randomized, single-blind, controlled study
Participants	**Setting:** 4 centres (3 Spain & 1 USA) **Inclusion criteria:** Mechanical ventilation for 24 hours and 18 years old **Exclusion criteria:** Respiratory infection, bronchiectasis, haematemesis, haemoptysis, or cystic fibrosis; sensitivity to silver or silver compounds; immunosuppression; and, in the substudy only, intubation within 30 days and pregnancy **Participant numbers:** 155 randomly assigned, 34 excluded (6 not intubated, 28 intubated < 24 h); 149 all intubated; 121 intubated ≥ 24 h analysed; 61 silver-coated ETT versus 60 non-coated ETT who were intubated for ≥ 24 h
Notes	Risk of VAP was not reported Cause of hospital mortality was not specified in this study

NCT000341354 2007

Methods	Unicentre, randomized, controlled study
Participants	**Setting:** San Gerardo Hospital in Milan, Italy **Inclusion criteria:** Adults at least 18 years old eligible for enrolment if they were expected to require mechanical ventilation with an endotracheal tube with an internal diameter of 7.5 mm or 8.0 mm for 48 hours or longer **Exclusion criteria:** Males and females less than 18 years old; patients who are expected to be intubated for less than 48 hours; patients who are allergic to silver-sulfadiazine; patients who require an endotracheal tube with an internal diameter less than 7.5 mm or greater than 8.0 mm; patients who do not tolerate disconnection from the ventilator; haemodynamically unstable; severe ARDS: $PaO_2/FiO_2 \leq 200$ at PEEP ≤ 5 cmH20 **Participant numbers:** not mentioned
Interventions	Silver-sulfadiazine tracheal tubes/mucus shaver in intubated patients expected to have a prolonged mechanical ventilation
Outcomes	No outcome data were available

信賴區間 & P值

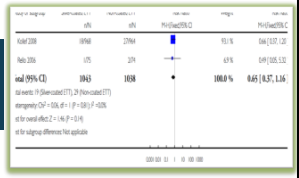
(一) 95%信賴區間:

- 該範圍代表有95%的機會涵蓋真正的療效。

(二) P值(<0.05):

- 比較兩組是否有顯著的差異，但只要樣本數夠大，就算只有些微差異也變得顯著，但**統計學上的顯著不一定代表臨床上有重大意義**。

森林圖



(一)森林圖:

- 中間會有一條垂直線 1表示 odd ratio (OR勝算比)=1或 relative risk (RR相對風險)=1，值落在 1的左邊表示風險降低，右邊表示風險增加，跨過 1表示沒有統計學上的差異。
- 每一條橫線表示一個研究結果的 95%信賴區間 (95%CI, 95% confidence interval)，有的會寬、有的會窄 (愈窄表示該研究越精確)。
- 橫線中間的正方形為點估計值，越大顆表示該值對此meta-analysis的貢獻度或權重 (weight)越高(樣本數愈大)。

異質性

(一)Chi-square test:

P<0.1 異質性過高➡個別分析評估異質性來源

(統計顯著水平通常設為 0.1, 因為異質性檢定的檢定力很低)

(二)異質程度: I^2

25%低的異質性；50%中的異質性；75%高的異質性

(三)眼球法:就是用眼睛看

看森林圖中各個研究的結果是分佈在同一邊或是不同邊，來判斷有無顯著異質性，但缺點就是缺乏客觀性。

結果 (Primary)

Risk of VAP at any time in patients intubated for ≥ 24 hours

Study or subgroup	Silver-coated ETT n/N	Non-coated ETT n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kollef 2008	37/766	56/743		100.0 %	0.64 [0.43, 0.96]
Total (95% CI)	**766**	**743**		**100.0 %**	**0.64 [0.43, 0.96]**

Total events: 37 (Silver-coated ETT), 56 (Non-coated ETT)

Heterogeneity: not applicable

Test for overall effect: Z = 2.16 (P = 0.030)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

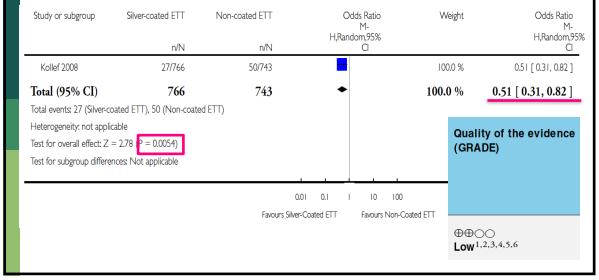
Favours Silver-coated ETT Favours Non-Coated ETT

Quality of the evidence (GRADE)

⊕⊕◯◯ Low[1,2,3,4,5,6]

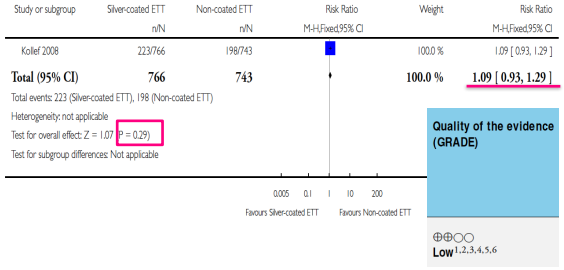
結果 (Primary)

Risk of VAP within 10 days of intubation in patients intubated for ≥ 24 hours



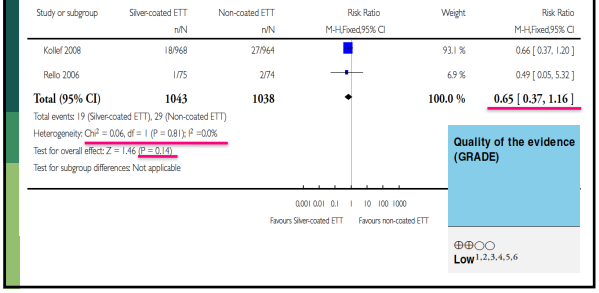
結果 (Primary)

Hospital mortality



結果 (Secondary)

Device-related adverse events



結果 (Secondary)

Duration of intubation

We observed no between-group differences with regards to duration of intubation (4.0 days, interquartile range (IQR) 1.9 to 7.9 days; P value = 0.59).

The overall duration of intubation in this study was less than 10 days.

結果 (Secondary)

Length of ICU and hospital stay

Silver-coated ETT was not associated with a significant reduction with regards to length of

Hospital stay (silver-coated ETT of 16 days (IQR 10.0 to 26.0 days) versus non-coated ETT of 16 days (IQR 10.0 to 27.0 days); P value = 0.57)

ICU stay (bothgroups: 8.0 days IQR 4.0 to 14.0 days; P value = 0.92) when compared with non-coated ETT.

結果 (Secondary)

Time to VAP onset

Silver-coated ETT was associated with a delayed time to VAP occurrence compared with non-coated ETT (hazard ratio 0.55,95% CI 0.37 to 0.84; P value = 0.006).

結果 (Secondary)

Cost-effectiveness of silver-coated ETTs

We included **no studies** with regards to cost effectiveness of silver-coated ETTs.

結論

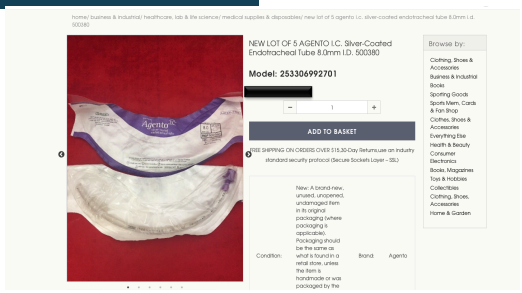
結論

- Silver-coated ETT seems to show a significant reduction with regards to the risk of VAP.
  (especially during the first 10 days and require MV for 24 hours.)
- Silver-coated ETT reduces time to VAP onset.
- The low quality of evidence, it is possible that the findings of this review could merely be a reflection of random error.

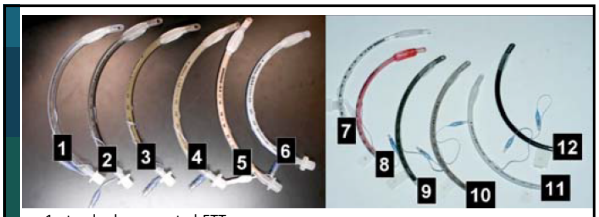
結論

- Investigators should rely on the same care bundles in clinical sites where patients will be included in order increase the precision of the estimate of treatment effect.

價錢



Thank you

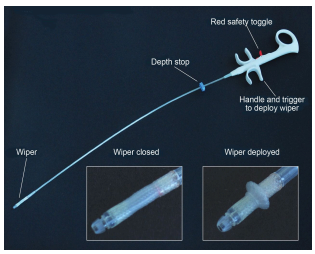


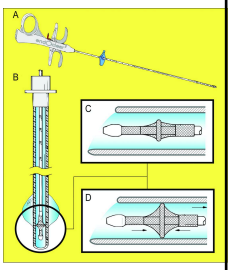
1. standard non-coated ETT
2. silver sulfadiazine chlorhexidine and carbon in polyurethane
3. silver sulfadiazine and carbon in polyurethane
4. silver sulfadiazine and chlorhexidine in polyurethane
5. silver sulfadiazine in polyurethane
6. chlorhexidine in polyurethane
7. standard non-coated ETT
8. rose Bengal for UV light
9. silver and carbon in polyurethane
10. silver in polyurethane
11. silver–platinum in polyurethane
12. silver–platinum and carbon in polyurethane

Cochrane

★可能降低證據品質 (Downgrading) 的因素及其解釋		
偏差風險 (Risk of bias)	考科藍合作組織偏差風險評估工具(The Cochrane Collaboration's tool for assessing risk of bias)評估的項目包括：隨機序列產生的方式(sequence generation)、分組隱匿(allocation concealment)、對受試者和研究人員及結果評估者實施盲法(blinding of participants, personnel and outcome assessors)、結果數據不完整(incomplete outcome data)及選擇性報告(selective outcome reporting)，以及其他未能分類的偏差(other bias)等。隨機序列產生的方式及分組隱匿用以評估是否產生選擇偏差(selection bias)、實施盲法用以評估是否產生表現性偏差(performance bias)、結果數據不完整則是評估是否出現失訪偏差(attrition bias)及報告偏差(reporting bias)，這些偏差的存在會影響文獻的品質(Higgins & Green, 2011)。未正確隨機分組、未進行分組隱匿、未實施盲法(特別是結果指標為主觀性指標、且其評估結果易受人為影響時)、研究失訪過多、未進行意向性分析、選擇性報告結果(尤其是僅報導觀測到有效結果的資料)、發現有療效後提前終止研究等，證據品質需降級。	Quality of the evidence (GRADE) ⊕⊕◯◯ Low[1,2,3,4,5,6]
不一致性 (Inconsistence)	1. Study design (-1): Single-blinded randomized controlled trial. 2. Low VAP rate. 3. No standardization of other contemporary VAP prevention strategies. 4. Inconsistency (-0): I^2 = 0%. 5. Publication bias (-0): Trial was registered.	
間接性 (Indirectness)	6. Imprecision (-1): Wide confidence intervals around the estimate of the effect. 融可進行二者之間療效的間接比較，但提供的證據品質比直接比較的隨機對照試驗要低。第二類間接證據包括人群、介入措施、對照措施、預期結果等存在間接性。	
不精確性 (Imprecision)	當研究納入的病人和觀察事件相對較少、而使得信賴區間較寬時，將降低其證據品質。	
發表偏差 (Publication bias)	若研究者未能發表研究(通常是顯示介入措施無效的研究)時，證據品質亦會減弱。典型情況是當公開的證據僅局限於少數試驗，而這些試驗全部由廠商贊助，此時應懷疑存在發表偏差。	

Mucus shaver





https://youtu.be/F9Oq2YBLo9I?t=821