

JOURNAL CLUB

Oxygen Saturation Target Range for Extremely Preterm Infants



報告人：新生兒加護病房

陳若蘋

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2014 JCR Science Edition

Rank in Category: **JAMA Pediatrics**

Journal Ranking

For **2014**, the journal **JAMA Pediatrics** has an Impact Factor of **7.148**.

This table shows the ranking of this journal in its subject categories based on Impact Factor.

Category Name	Total Journals in Category	Journal Rank in Category	Quartile in Category
PEDIATRICS	119	2	Q1

前言

- 雖然氧氣是生存的關鍵，但過多的氧氣可能是有害的
- 氧氣治療併發症中最廣為人知的，特別是對於出生週數不足28週的嬰兒，是早產兒視網膜病變(ROP)
- 1940和1950年初，氧氣大量的使用，造成ROP盛行。因此導致了極為謹慎、限制氧氣的使用，在臨床上可以耐受早產兒缺氧，但這又引起死亡率增加

前言

- 因此，監測和保持最佳的血氧飽和度，是治療呼吸系統疾病的重要部分
- 2007年，美國小兒科學會建議，血氧飽和度85%~95%，氧分壓50~80mmHg
- 2010年，歐洲指南建議，血氧飽和度的範圍從85%~93%，上限為95%

研究目的

- 系統性地檢視證據，以評估有限制的 (restricted; SpO₂ 85%-89%) 或自由的 (liberal; SpO₂ 91%-95%) 使用氧氣，對早產兒合併症發生率及死亡率的影響

步驟1 研究探討的問題為何？

研究族群 / 問題 (Population/ Problem)	出生周數小於28周的早產兒
介入措施 (Intervention)	限制性的給氧 (SpO ₂ , 85%–89%)
比較 (Comparison)	自由的給氧 (SpO ₂ , 91%–95%)
結果 (Outcomes)	出院前死亡、24個月前死亡及嚴重失能、24個月前死亡、神經發展狀況、聽力喪失、支氣管肺發育不良、壞死性腸炎、早產兒視網膜病變

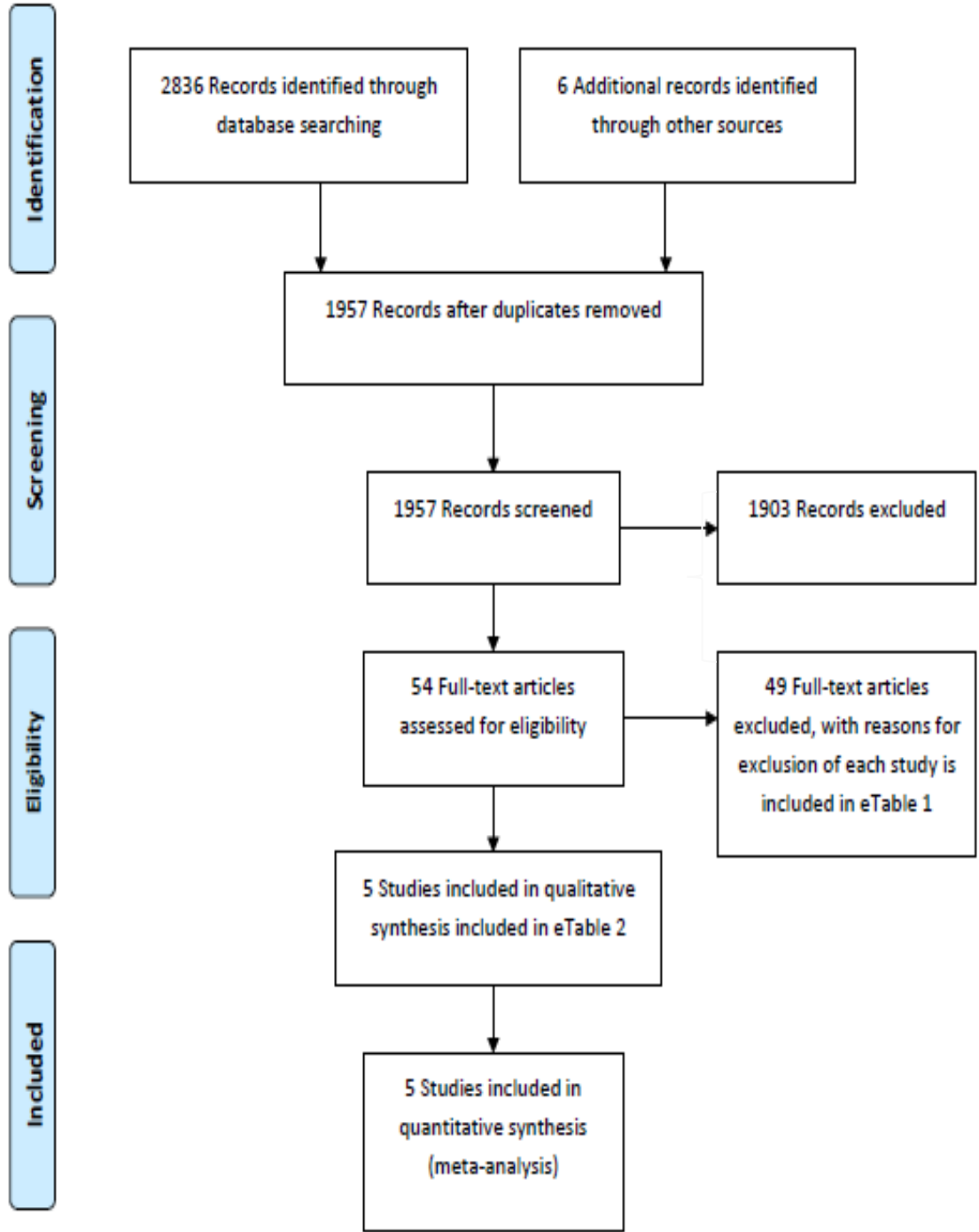
步驟2 系統性文獻回顧的品質如何？(FAITH)

Find - 研究是否找到所有的相關證據

良好的文獻搜尋至少應包括二個主要的資料庫(如：Medline, Cochrane考科藍實證醫學資料庫, EMBASE 等)，並且加上文獻引用檢索(參考文獻中相關研究、Web of Science, Scopus 或 Google Scholar)、試驗登錄資料等。文獻搜尋應不只限於英文，並且應同時使用 MeSH字串及一般檢索詞彙(text words)。

- 搜尋MEDLINE, PubMed, CENTRAL, and CINAHL 資料庫，從成立以來至2014年3月31日止
- 美國兒科醫學會2000~2014接受的摘要
- 沒有語言及時間的限制
- 每一篇研究相關的參考文獻及書目引用資料
- ClinicalTrial.gov(未完成的臨床試驗)

評讀結果：✓是 ☐否 ☐不清楚⁷



步驟2 系統性文獻回顧的品質如何？(FAITH)

Appraisal - 文獻是否經過嚴格評讀

應根據不同臨床問題的文章類型，選擇適合的評讀工具，並說明每篇研究的品質(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)

- 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
- 本篇所納入分析的文章都屬於低風險

評讀結果：✓是 ☐否 ☐不清楚

考科藍誤差風險評估工具

- 分派順序的產生
 - generation of the allocation sequence
- 分派順序的保密
 - concealment of the allocation sequence
- 受試者與研究者盲性
 - blinding of participants and researchers
- 預後評估者的盲性
 - blinding of outcome assessment
- 不完整的研究結果報告
 - incomplete outcome data
- 選擇性報告
 - selective reporting
- 其他誤差
 - other bias

步驟2 系統性文獻回顧的品質如何？(FAITH)

Included - 是否只納入具良好效度的文章

僅進行文獻判讀是不足夠，系統性文獻回顧只納入至少要有一項研究結果是極小偏誤的試驗。

- 使用GRADE進行證據品質的評比
- GRADE是一個整合證據與制定臨床建議的工具
 - 以結果(outcome)為中心，擷取不同研究的同一結果(a body of evidence)進行評等
 - 根據五項降級因素，以及三項升級因素，評定每個結果的證據品質
 - 對於治療類問題而言
 - 根據隨機對照研究結果完成的結果分析（一般是藉由系統性文獻回顧），一開始可以列在high quality
 - 根據觀察型研究的結果完成的結果分析一開始只能列在low quality

步驟2 系統性文獻回顧的品質如何？(FAITH)

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五項降級因素：

- 研究的限制 (Risk of bias)
- 結果不一致(Inconsistency)
- 研究的不直接性(Indirectness)
- 研究的不精確性(Imprecision)
- 發表偏誤(Publication bias)

步驟2 系統性文獻回顧的品質如何？(FAITH)

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三項升級因素：

- 效果非常顯著 (large effect)
- 劑量效應(dose response)
- 干擾因素妥善處理，且不致影響結論

根據結果的重要性，擬定證據等級(level of evidence：分為high, moderate, low, very low)及其建議強度 (recommendation strength：分為strong 及weak)

步驟2 系統性文獻回顧的品質如何？(FAITH)

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Table. GRADE Summary of Findings of Restricted vs Liberal Oxygen Exposure for Extremely Premature Infants

Outcomes	No. of Cases per 1000 Infants		RR (95% CI)	Participants, No.	Studies, No.	Quality of Evidence ^b
	Assumed Risk of Liberal Oxygen Exposure ^a	Corresponding Risk of Restricted Oxygen Exposure ^a (95% CI)				
Death before hospital discharge	165	194 (170-224)	1.18 (1.03-1.36)	3757	4	Low ^{c,d,e,f}
Death or disability at 24 mo	390	398 (367-445)	1.02 (0.94-1.14)	2716	3	Moderate ^{c,d}
Death before 24 mo	167	194 (164-229)	1.16 (0.98-1.37)	2783	3	Moderate ^{c,d}
Bronchopulmonary dysplasia	397	377 (345-413)	0.95 (0.87-1.04)	2869	5	Moderate ^{c,d}
Neurodevelopmental outcomes at 18-24 mo	53	55 (39-78)	1.03 (0.73-1.45)	2252	3	Moderate ^{c,d}
Hearing loss	22	29 (17-49)	1.32 (0.78-2.21)	2237	3	Moderate ^{c,d}
Necrotizing enterocolitis	90	112 (95-133)	1.24 (1.05-1.47)	4929	5	Moderate ^{c,d}
Retinopathy of prematurity	145	104 (72-151)	0.72 (0.5-1.04)	4066	5	Low ^{c,d,g}

評讀結果：□是 ✓否 □不清楚 14

步驟2 系統性文獻回顧的品質如何？(FAITH)

Total up - 作者是否以表格和圖表「總結」試驗結果

應該用至少 1 個摘要表格呈現所納入的試驗結果。若結果相近，可針對結果進行統合分析 (meta-analysis)，並以「森林圖」(forest plot) 呈現研究結果，最好再加上異質性分析

Figure 2. Mortality Associated With Restrictive or Liberal Use of Oxygen

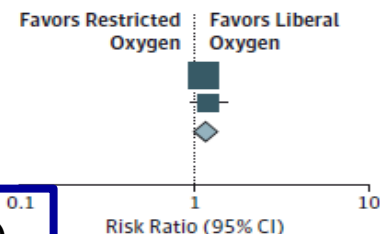
A Death to hospital discharge

Study or Subgroup	Restricted Oxygen, No.		Liberal Oxygen, No.		Weight, %	Risk Ratio (95% CI)
	Events	Total	Events	Total		
BOOST II trial, ¹⁵ 2013	235	1221	203	1220	65.0	1.16 (0.98-1.37)
SUPPORT II trial, ¹³ 2010	130	654	107	662	35.0	1.23 (0.98-1.55)
Total (95% CI)		1875		1882	100.0	1.18 (1.03-1.36)
Total events	365		310			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.17$, $df = 1$ ($P = .68$); $I^2 = 0\%$

Test for overall effect: $z = 2.39$ ($P = .02$)

1.18 (1.03-1.36)

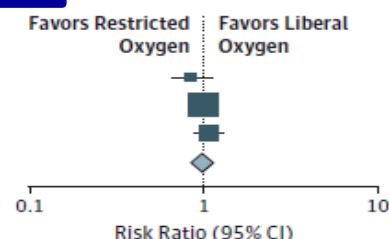


B Death or severe disability before 18-24 mo

Study or Subgroup	Restricted Oxygen, No.		Liberal Oxygen, No.		Weight, %	Risk Ratio (95% CI)
	Events	Total	Events	Total		
BOOST II-New Zealand trial, ²⁹ 2014	65	167	76	168	15.7	0.86 (0.67-1.11)
COT, ¹² 2013	298	578	283	569	54.9	1.04 (0.92-1.16)
SUPPORT, ²⁸ 2012	185	612	171	622	29.4	1.10 (0.92-1.31)
Total (95% CI)		1357		1359	100.0	1.02 (0.92-1.14)
Total events	548		530			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.49$, $df = 2$ ($P = .29$); $I^2 = 20\%$

Test for overall effect: $z = 0.44$ ($P = .66$)

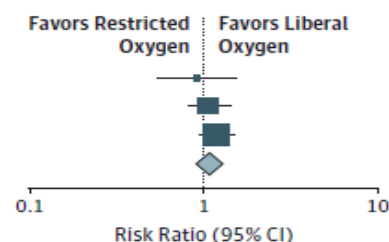


C Death before 18-24 mo

Study or Subgroup	Restricted Oxygen, No.		Liberal Oxygen, No.		Weight, %	Risk Ratio (95% CI)
	Events	Total	Events	Total		
BOOST II-New Zealand trial, ²⁹ 2014	25	170	27	170	10.2	0.93 (0.56-1.53)
COT, ¹² 2013	97	585	88	577	36.5	1.09 (0.83-1.42)
SUPPORT, ²⁸ 2012	140	633	118	648	53.3	1.21 (0.98-1.51)
Total (95% CI)		1388		1395	100.0	1.13 (0.97-1.33)
Total events	262		233			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.10$, $df = 2$ ($P = .58$); $I^2 = 0\%$

Test for overall effect: $z = 1.55$ ($P = .12$)



步驟2 系統性文獻回顧的品質如何？(FAITH)

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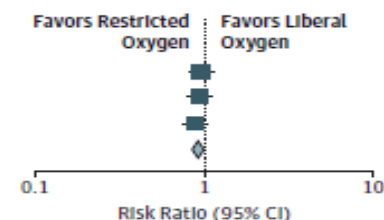
Figure 3. Morbidity Associated With Restrictive or Liberal Use of Oxygen: Bronchopulmonary Dysplasia, Necrotizing Enterocolitis, and Neurodevelopmental Outcomes

A Bronchopulmonary dysplasia at 36 wk

Study or Subgroup	Events	Restricted Oxygen, No. Total	Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II trial, ¹⁵ 2013	160	353	172	376	33.2	0.99 (0.85-1.16)
COT, ¹² 2013	164	515	171	517	27.0	0.96 (0.81-1.15)
SUPPORT, ¹³ 2010	205	540	237	568	39.8	0.91 (0.79-1.05)
Total (95% CI)		1408		1461	100.0	0.95 (0.87-1.04)
Total events	529		580			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.63$, $df = 2$ ($P = .73$); $I^2 = 20\%$

Test for overall effect: $z = 1.09$ ($P = .28$)

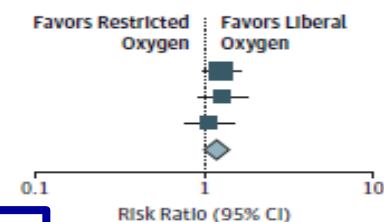


B Necrotizing enterocolitis

Study or Subgroup	Events	Restricted Oxygen, No. Total	Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II trial, ¹⁵ 2013	127	1221	97	1217	44.1	1.30 (1.01-1.68)
COT, ¹² 2013	74	602	56	599	26.0	1.31 (0.95-1.83)
SUPPORT, ¹³ 2010	76	641	70	649	29.9	1.10 (0.81-1.49)
Total (95% CI)		2464		2465	100.0	1.24 (1.05-1.47)
Total events	277		223			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.88$, $df = 2$ ($P = .65$); $I^2 = 0\%$

Test for overall effect: $z = 2.54$ ($P = .001$)



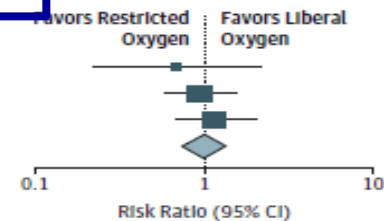
1.24 (1.05-1.47)

C Neurodevelopmental outcomes (GMFCS score ≥ 2)

Study or Subgroup	Events	Restricted Oxygen, No. Total	Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II-New Zealand trial, ²⁹ 2014	5	144	7	142	9.5	0.70 (0.23-2.17)
COT, ¹² 2013	30	488	31	488	50.6	0.97 (0.60-1.57)
SUPPORT, ¹³ 2012	26	479	23	511	39.9	1.21 (0.70-2.08)
Total (95% CI)		1111		1141	100.0	1.03 (0.73-1.45)
Total events	61		61			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.82$, $df = 2$ ($P = .66$); $I^2 = 0\%$

Test for overall effect: $z = 0.14$ ($P = .89$)



步驟2 系統性文獻回顧的品質如何？(FAITH)

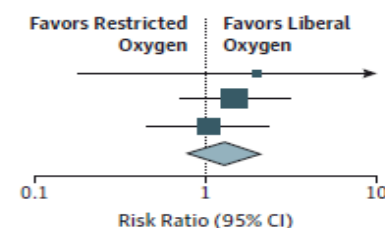
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Figure 4. Morbidity Associated With Restrictive or Liberal Use of Oxygen: Hearing Loss/Impairment and Retinopathy of Prematurity

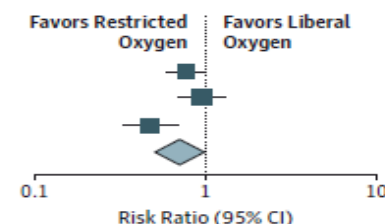
A Hearing loss/impairment

Study or Subgroup	Restricted Oxygen, No.		Liberal Oxygen, No.		Weight, %	Risk Ratio (95% CI)
	Events	Total	Events	Total		
BOOST II-New Zealand trial, ²⁹ 2014	2	135	1	136	4.7	2.01 (0.18-21.96)
COT, ¹² 2013	18	487	12	489	52.1	1.51 (0.73-3.09)
SUPPORT, ¹³ 2012	12	479	12	511	43.2	1.07 (0.48-2.35)
Total (95% CI)		1101		1136	100.0	1.32 (0.78-2.21)
Total events	32		25			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.53$, $df = 2$ ($P = .77$); $I^2 = 0\%$ Test for overall effect: $z = 1.04$ ($P = .30$)						



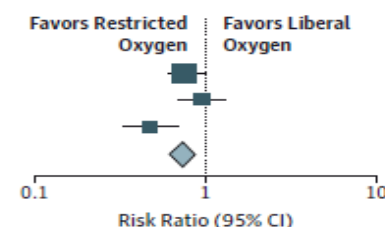
B Retinopathy of prematurity

Study or Subgroup	Restricted Oxygen, No.		Liberal Oxygen, No.		Weight, %	Risk Ratio (95% CI)
	Events	Total	Events	Total		
BOOST II trial, ¹⁵ 2013	110	1035	141	1044	36.6	0.79 (0.62-0.99)
COT, ¹² 2013	64	500	66	503	32.3	0.98 (0.71-1.34)
SUPPORT, ¹³ 2012	41	475	91	509	31.0	0.48 (0.34-0.68)
Total (95% CI)		2010		2056	100.0	0.72 (0.50-1.04)
Total events	215		298			
Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 8.93$, $df = 2$ ($P = .01$); $I^2 = 78\%$ Test for overall effect: $z = 1.73$ ($P = .08$)						



C Retinopathy of prematurity using a fixed-effects model

Study or Subgroup	Restricted Oxygen, No.		Liberal Oxygen, No.		Weight, %	Risk Ratio (95% CI)
	Events	Total	Events	Total		
BOOST II trial, ¹⁵ 2013	110	1035	141	1044	50.3	0.79 (0.62-0.99)
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SUPPORT, ¹³ 2012	41	475	91	509	22.9	0.48 (0.34-0.68)
Total (95% CI)		2010		2056	100.0	0.75 (0.63-0.88)
Total events	215		298			
Heterogeneity: $\chi^2 = 8.93$, $df = 2$ ($P = .01$); $I^2 = 78\%$ Test for overall effect: $z = 3.47$ ($P = .001$)						



評讀結果：✓是 □否 □不清楚

步驟2 系統性文獻回顧的品質如何？(FAITH)

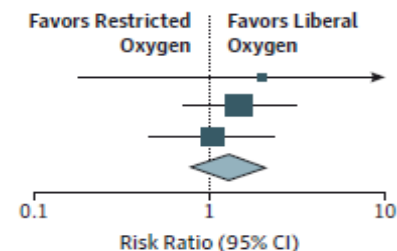
Heterogeneity異質性 - 試驗的結果是否相近

在理想情況下，各個試驗的結果應相近或具同質性，若具有異質性，作者應評估差異是否顯著(卡方檢定)。根據每篇個別研究中不同的PICO及研究方法，探討造成異質性的原因。

Figure 4. Morbidity Associated With Restrictive or Liberal Use of Oxygen: Hearing Loss/Impairment and Retinopathy of Prematurity

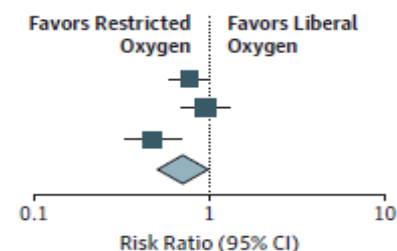
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Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.53$, $df = 2$ ($P = .77$); $I^2 = 0\%$						
Test for overall effect: $z = 1.04$ ($P = .30$)						



B Retinopathy of prematurity

Study or Subgroup	Restricted Oxygen, No.		Liberal Oxygen, No.		Weight, %	Risk Ratio (95% CI)
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Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 8.93$, $df = 2$ ($P = .01$); $I^2 = 78\%$						
Test for overall effect: $z = 1.73$ ($P = .08$)						



評讀結果：✓是 □否 □不清楚 18

結果為何？

使用何種評估方式，療效有多大（是否來自隨機效果）？

- 對多數的結果(支氣管肺發育不良、神經發展狀況、聽力喪失、早產兒視網膜病變)而言，兩組間的風險無顯著差異
- 限制氧氣使用組，出院前死亡率及發生壞死性腸炎風險較高，但前者利用GRADE標準，證據品質評比很低



國內意見

- 為避免抗氧化能力不成熟的早產兒，暴露在過多的氧氣及持續的氧化壓力，在早產兒出生後的前面幾週，若維持85－95%較低的血氧濃度，可以減少常見合併症的發生率。

袁朝蓉, 華一鳴, & 李慈音. (2009). 從氧化壓力重新思考早產兒氧氣的使用. *護理雜誌*, 56(4), 77-82

- 現況：警告上下限設定：90~100%
- 問題：早產兒是否應限制血氧飽和度不超過98%？
 - 若班內監測值均>98%，應積極調整呼吸器設定或給氧濃度



同意(21)

懷疑(5)



thank you!