Evidence Synthesis Primer (Part 2) – Evaluating Research Evidence: A How-To Guide

Presentation will begin at 12:00 PM (PT)

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1

Research Support Services: Members gain access to the different research services, resources, and tools offered by ITHS, including the ITHS Research Navigator.

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Contact our Director of Research Development



- **Project Consultation**
- Strategic Direction
- **Resources and Networking**

Melissa D. Vaught, Ph.D. ithsnav@uw.edu 206.616.3875

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Feedback

At the end of the seminar, a link to the feedback survey will be sent to the email address you used to register.



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Evidence Synthesis Primer (Part 2) – Evaluating Research Evidence: A How-To Guide

Presented by Kenn B. Daratha, PhD

Providence Sacred Heart Medical Center Gonzaga University Nurse Anesthesia Program





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Learning Objectives

Attendees will be able to :



Conduct an a-priori power analysis



Critically evaluate a treatment study



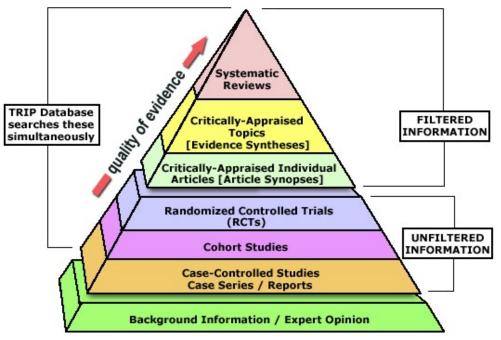
Clinical Questions

Most clinical questions arise when observing variability in practice:

- Long held beliefs
- Learned during our training
- Success stories of our colleagues
- Publication
- We have always done it that way
- Compelling evidence forces us to consider an intervention



Evidence Pyramid



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Evidence Synthesis Primer (Part 1)

- Clinical Question (PICO Format)
- Cochrane Review Groups
- Medline Searches (MeSH Terms)
- Evidence Catalogs
- Evidence Flow Diagrams
- Summary Table of Evidence
- Evidence Synthesis



Critically Appraised Topic



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Evidence Synthesis Primer (Part 2)

Reviewer Name:	Answer Key	
Review Date:	05/21/2020	
PMID:	32160661 (Barrot)	
Journal Article Title:	Liberal or Conservat Syndrome, (2020)	ive Oxygen Therapy for Acute Respiratory Distress
Clinical Question:	Among patients with acute respiratory distress syndrome (ARDS) does conservative vs. liberal oxygen therapy improve all-cause mortality at 28	
Clinical Question Type:	days.	
	 Diagnosis Prognosis 	
Church Devices		iew/Meta-Analysis
Study Design:	Prospective, randon	nized open label study.
Sample Size and Power:	850 patients 90% between group a priori power analysis based on an expected ef size of 9% from published results of two prospective trials 396 were eligible, 191 were excluded: 205 randomized Trial stopped by the DSMB for increased adverse risk in the conserva oxygenation group.	
Validity Assessment:	Criteria	Assessment
Calendarii dhe 🝷 de de doministra fonderi de	Randomization	Computer randomization stratified by center, age, and severity of respiratory failure
	Blinding	Open Label (not blinded based on impossibility of making treatment assignment)
	Baseline Group Comparability	Groups were comparable based on review of Table 1
	Follow up	Survival curves indicate patients were followed up to 90 days after surgery. Four patients our of 205 randomized were excluded from analysis (2%).
	Intent to Treat	Analyses were performed in the intention to treat population, defined as all patients who underwent randomization minus exclusions.
Validity Summary:	and intent to treat, practice. While the	domization, baseline group comparability, follow up this study was determined valid for informing study was not blinded, the open label nature of this likely change study outcomes.

- Read and assess each full-text article you have chosen to include in your review
- I record my assessment findings in a critically appraised topic (CAT)
- Assess design, power, study validity (five criteria) and clinical importance of study findings



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Evidence Synthesis Primer (Part 2)

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PMID:	32160661 (Barrot)		
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	Syndrome. (2020)		
Clinical Question:		h acute respiratory distress syndrome (ARDS) does eral oxygen therapy improve all-cause mortality at 28	
Clinical Question Type:	Treatment		
onnear question rype.	Diagnosis		
	Prognosis		
		view/Meta-Analysis	
Study Decige:			
Study Design:	Prospective, randor	nized open label study.	
Sample Size and Power:	850 patients 90% between group a priori power analysis based on an expected effect		
	size of 9% from published results of two prospective trials		
	396 were eligible, 191 were excluded: 205 randomized		
	Trial stopped by the DSMB for increased adverse risk in the conservative		
	oxygenation group.		
Validity Assessment:	Criteria	Assessment	
	Randomization	Computer randomization stratified by center, age, and severity of respiratory failure	
	Blinding	Open Label (not blinded based on impossibility of making treatment assignment)	
	Baseline Group	Groups were comparable based on review of	
	Comparability	Table 1	
	Follow up	Survival curves indicate patients were followed	
		up to 90 days after surgery. Four patients our of 205 randomized were excluded from analysis	
		(2%).	
	Intent to Treat	Analyses were performed in the intention to	
		treat population, defined as all patients who underwent randomization minus exclusions.	
Validity Summary:		domization, baseline group comparability, follow up	
		this study was determined valid for informing	
	practice. While the study was not blinded, the open label nature of this		
	experiment did not likely change study outcomes.		

- Sample Size and Power
- Randomization
- Blinding
- Baseline Group Comparability
- Follow-Up
- Intent to Treat



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Sample Size & Power

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Statistical Power

• Definition: The ability to detect differences in groups (effect) if a difference exists.



	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	
Sampling Indicates No Group Differences		

If group differences exist and our sampling evidence says so, we are correct.



	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	
Sampling Indicates No Group Differences		Correct

If group differences do not exist and our sampling evidence says so, we are correct.



	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	Type I Error (α)
Sampling Indicates No Group Differences		Correct

If sampling tells us group differences exist but in truth they do not, we have made an error.



	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	Type I Error (α)
Sampling Indicates No Group Differences	Type II Error (β)	Correct

If sampling tells us no group differences exist but in truth they do, we have made an error.



	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	Type I Error (α)
Sampling Indicates No Group Differences	Type II Error (β)	Correct

Complete framework for how sampling evidence relates to unknown truth.



Truth – Yes Group Differences	Truth – No Group Differences
Correct	Type I Error (α)
Type II Error (β)	Correct
	Differences Correct Type II Error

Focus now on the truth – that group differences in fact exist.



n – Yes Group rences	Truth – No Group Differences
Correct	Type I Error (α)
Type II Error (β)	Correct
	rences

Group differences exist, but our sampling evidence tells us group differences do not exist. The probability of a type II error is denoted by β .



 $(1-\beta) + (\beta) = 1$

es Differences
prrect Type I Error 1-β) (α)
Il Error Correct (β)

Group differences exist, and our sampling evidence tells us group differences do exist. The probability of correctly identifying group differences if they exist is 1- β .

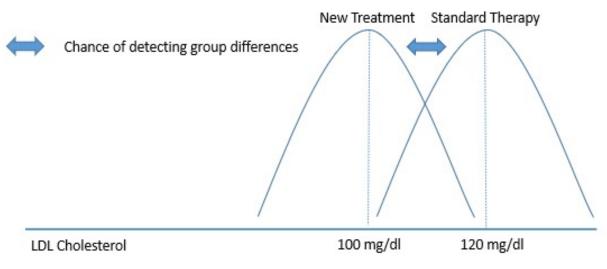


What Influences Power?

- Power is the ability to detect group differences (effect), if differences exist
- So, what influences power?



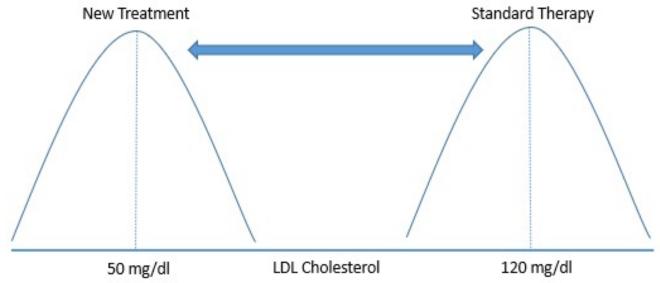
What Influences Power?



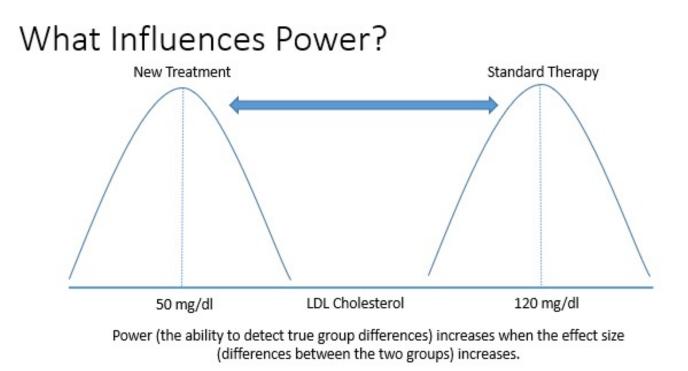




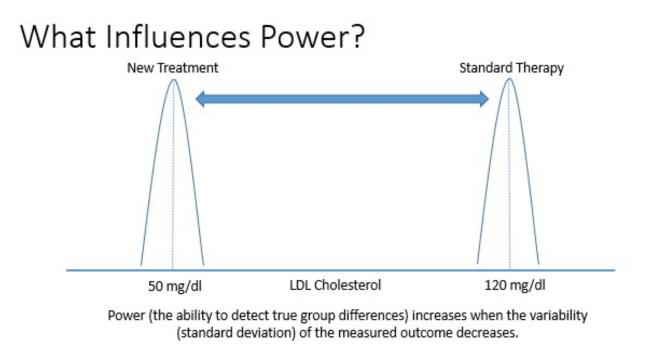
What Influences Power?



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What Influences Power?

- Power is the ability to detect group differences (effect), if differences exist
- So, what influences power?
 - Power increases when effect size increases
 - Power increases when variability decreases



What Influences Power?

- Power is the ability to detect group differences (effect), if differences exist
- So, what influences power?
 - Perhaps most intuitive the more we know, the greater the probability of detecting true group differences.
 - We know more about a population by increasing the sample size!

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What Influences Power?

- Power is the ability to detect group differences (effect), if differences exist
- So, what influences power?
 - Power increases when effect size increases
 - Power increases when variability decreases
 - Power increases as sample size increases



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Central and noncentral distributions	Protocol of pov	ver analyses		
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Test family Statistical test				
χ^2 tests \vee Goodness-of-fit t	tests: Continger	ncy tables		~
Type of power analysis				
A priori: Compute required sample siz	ze – given α, po	wer, and effect size		~
Input Parameters		Output Parameters		
Determine => Effect size w	0.3	Noncentrality parameter λ	7.92000	000
α err prob	0.05	Critical X ²	3.84145	88
α err prob Power (1-β err prob)	0.05 .80	Critical X ²	3.84145	88 88
			3.84145 0.80352	88
Power (1-β err prob)	.80	Total sample size		88

- G*Power

 (<u>https://www.psychologie.hhu.de/arbeitsgruppen/al</u> lgemeine-psychologie-undarbeitspsychologie/gpower)
- Chi-Square Analysis
- Effect Size (Moderate)
- Alpha = 0.05
- Beta = 0.20
- DF = 1

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BACKGROUND

In patients with acute respiratory distress syndrome (ARDS), the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network recommends a target partial pressure of arterial oxygen (Pao₂) between 55 and 80 mm Hg. Prospective validation of this range in patients with ARDS is lacking. We hypothesized that targeting the lower limit of this range would improve outcomes in patients with ARDS.

METHODS

In this multicenter, randomized trial, we assigned patients with ARDS to receive either conservative oxygen therapy (target Pao₂, 55 to 70 mm Hg; oxygen saturation as measured by pulse oximetry [Spo₂], 88 to 92%) or liberal oxygen therapy (target Pao₂, 90 to 105 mm Hg; Spo₂, ≥96%) for 7 days. The same mechanical-ventilation strategies were used in both groups. The primary outcome was death from any cause at 28 days.

RESULTS

After the enrollment of 205 patients, the trial was prematurely stopped by the data and safety monitoring board because of safety concerns and a low likelihood of a significant difference between the two groups in the primary outcome. Four patients who did not meet the eligibility criteria were excluded. At day 28, a total of 34 of 99 patients (34.3%) in the conservative-oxygen group and 27 of 102 patients (26.5%) in the liberal-oxygen group had died (difference, 7.8 percentage points; 95% confidence interval [CI], -4.8 to 20.6). At day 90, 44.4% of the patients in the conservative-oxygen group and 30.4% of the patients in the liberal-oxygen group had died (difference, 14.0 percentage points; 95% CI, 0.7 to 27.2). Five mesenteric ischemic events occurred in the conservative-oxygen group.

CONCLUSIONS

Among patients with ARDS, early exposure to a conservative-oxygenation strategy with a Pao₂ between 55 and 70 mm Hg did not increase survival at 28 days. (Funded by the French Ministry of Health; LOCO₂ ClinicalTrials.gov number, NCT02713451.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome

 Loic Barrot, M.D., Pierre Asfar, M.D., Ph.D., Frederic Mauny, M.D., Ph.D., Hadrien Winiszewski, M.D., Florent Montini, M.D., Julio Badie, M.D., Jean-Pierre Quenot, M.D., Ph.D., Sebastien Pili-Floury, M.D., Ph.D., Belaid Bouhemad, M.D., Ph.D., Guillaume Louis, M.D., Bertrand Souweine, M.D., Ph.D., Olivier Collange, M.D., Ph.D., Julien Pottecher, M.D., Ph.D., Bruno Levy, M.D., Ph.D., Marc Puyraveau, M.Sc., Lucie Vettoretti, Ph.D., Jean-Michel Constantin, M.D., Ph.D., and Gilles Capellier, M.D., Ph.D., for the LOCO₂ Investigators and REVA Research Network*



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Power & Sample Size



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Randomization

The NEW ENGLAND JOURNAL of MEDICINE

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METHODS

In this multicenter, randomized trial, we assigned patients with ARDS to receive N Engl J Med 2020;382:999-1008 In this multicenter, randomized trial, we assigned patients with AKUS to receive $w_{16g}/J \omega at most of the conservative oxygen therapy (target Pao, 55 to 70 mm Hig, oxygen statistic). To halse, fully as measured by pulse oximitery (5po,1 & 8t o 25%) or liberal oxygen therapy (target Pao, 90 to 105 mm Hig, Spo, 25%) for 7 days. The same mechanical ventilation strategies were used in both groups. The primary outcome was death from any$ cause at 28 days.

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N ENGL J MED 382;11 NEJM.ORG MARCH 12, 2020

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- · Search for the term 'power'
- Methods Statistical Analysis •
 - We performed a power calculation with the published results of two available prospective trials on oxygen targets in ICU populations.
 - We determined that the inclusion of 850 patients would provide a power of 90% to show an absolute between-group difference of 9 percentage points in the primary outcome, assuming a death rate of 30% at day 28 in the liberal-oxygen group, a one-sided test, and a significance level of 0.05.

Randomization



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Randomization

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METHODS

METHODS In this multicenter, randomized trial, we assigned patients with ARDS to receive N Engl J Med 2020;382-999.1008.

After the enrollment of 205 patients, the trial was prematurely stopped by the data and safety monitoring board because of safety concerns and a low likelihood of a and safety monitoring board because of safety concerns and a low likelihood of a significant difference between the two groups in the primary outcome. Four pa-tients who did not meet the eligibility criteria were excluded. At day 28, a total of 40 of 99 patients (34-5%) in the conservative-oxygen group and 27 of 102 patients (26.5%) in the liberal-oxygen group had died (difference, 7.8 percentage points; 9%) confidence interval (121, -4.8 to 20.6). At day 90, 44.4% of the patients in the conservative-oxygen group and 30.4% of the patients in the liberal-oxygen group and 30.4% of the patience, 14.0 percentage points; 9% C, 0.7 to 72.3. Five mesenteric ischemic events occurred in the conservative-oxygen group.

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- Search for the term 'random'
- Trial Procedures
 - Randomization was stratified • according to center, age, and severity of respiratory failure according to PaO2:FiO2, with a PEEP of 5 cm of water and a FiO2 of 60 to 100%. Computer randomization was performed in blocks of four.

Blinding

Blinding



ORIGINAL ARTICLE

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METHODS

METHODS In this multicenter, randomized trial, we assigned patients with ARDS to receive N Engl J Med 2020;382-999.1008. in this multicenter, randomized trial, we assigned platents with ARUS to receive a long load 20203229931088. either conservative orogen therapy (target Plan, 55 to 752k) or liberal orgen therapy (target Plan), and therapy of the Research Plate and the second standard more place on the Higs Place 2020 (for 7 days. The same mechanical-level initial on strategies were used in both groups. The primary outcome was death from any cause at 28 dys.

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- Search for the term 'blind' or 'conceal'
- Trial Procedures
 - This was an open-label trail • because of the impossibility of masking treatment assignments with the use of SpO2 and PaO2 monitoring in the ICU.

Baseline Group Comparability



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Baseline Group Comparability

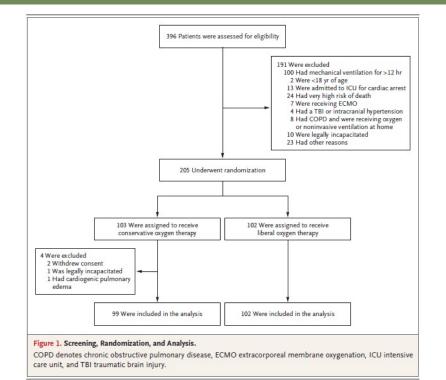
Characteristic	Conservative Oxygen (N = 99)	Liberal Oxygen (N = 102)
Age — yr	63.0±15.5	63.5±14.5
Male sex — no. (%)	65 (65.7)	64 (62.7)
BMI†	27.9±7.2	27.9±6.6
Tidal volume — ml/kg of predicted body weight‡	6.0±0.3	6.2±0.5
Minute ventilation — liters/min	9.4±2.1	9.6±2.1
PEEP — cm of water	6.2±2.7	6.4±3.5
Plateau pressure — cm of water	19.8±5.1	20.8±4.8
Respiratory-system compliance — ml/cm of water	31.1±11.86	28.6±8.99
Pao₂:Fio₂ — mm Hg§	116.8±47.4	120.1±53.6
Pao ₂ — mm Hg	90.3±38.8	92.3±44.8
Fio ₂ (%)	80.3±18.4	80.1±19.2
Use of catecholamines — no. (%)	70 (70.7)	73 (71.6)
Arterial pH	7.31±0.11	7.31±0.1
Lactate level — mmol/liter	2.2±1.4	2.6±2.2
Hemoglobin level — g/liter	113±25	118±24
SAPS III¶	66.9±13.7	67.9±14.4
SOFA score	9.3±3.68	8.9±3.6
Main cause of ARDS		
Pulmonary	78 (78.8)	74 (72.5)
Extrapulmonary	21 (21.2)	28 (27.5)

- Review Table 1
- How well are study participants matched between the conservative and liberal oxygen groups?



Follow-Up

Follow-up



- Review Figure 1
- Were patients followed long enough for the outcome to occur?
- Did 80% of patients enrolled in the trial complete the trial?



Intent to Treat

Intent to Treat

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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ABSTRACT

BACKGROUND

In patients with acute respiratory distress syndrome (ARDS), the National Heart, The authors In patients with acute respiratory distress syndrome (ARDS), the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network recommends a target DC. capellier at Reasimation Medical In partial pressure of arterial oxygen (Pao,) between 55 and 80 mm Hg. Prospective correction of the second output with ARDS. A complete list of investigators in th

HETHODS

METHODS In this multicenter, randomized trial, we assigned patients with ARDS to receive N Engl J Med 2020;382-999.1008. In this multicenter, randomized trial, we assigned patients with AKDS to receive N_{tog} [Med 2005;15:203-either conservative excigent herait (larger Plax, 55 to 70 mm Hg, acygens attaution to 00-1035) (Significantified as measured by pulse oximetry [Spc], 88 to 92%) or liberal oxygen herapy (larger $O_{\text{cons}} = 0.223)$ (Significantified as measured by pulse oximetry [Spc], 28 to 92%) or liberal oxygen herapy (larger $O_{\text{cons}} = 0.223)$ (Significantified as measured by pulse oximetry [Spc], 28 to 92%) or liberal oxygen herapy (larger $O_{\text{cons}} = 0.223)$ (Significantified as measured by pulse oximetry [Spc], 28 to 92%) or liberal oxygen herapy (larger $O_{\text{cons}} = 0.223)$ (Significantified as measured by pulse oximetry [Spc], 2005) (Signif cause at 28 days.

After the enrollment of 205 patients, the trial was prematurely stopped by the data and safety monitoring board because of safety concerns and a low likelihood of a and safety monitoring board because of safety concerns and a low likelihood of a significant difference between the two groups in the primary outcome. Four pa-tients who did not meet the eligibility criteria were excluded. At day 28, a total of 40 of 99 patients (34-5%) in the conservative-oxygen group and 27 of 102 patients (26.5%) in the liberal-oxygen group had died (difference, 7.8 percentage points; 9%) confidence interval (121, -4.8 to 20.6). At day 90, 44.4% of the patients in the conservative-oxygen group and 30.4% of the patients in the liberal-oxygen group and 30.4% of the patience, 14.0 percentage points; 9% C, 0.7 to 72.3. Five mesenteric ischemic events occurred in the conservative-oxygen group.

CONCLUSIONS

Among patients with ARDS, early exposure to a conservative-oxygenation strategy with a Pao, between 55 and 70 mm Hg did not increase survival at 28 days. (Funded by the French Ministry of Health; LOCO, ClinicalTrials.gov number, NCT02713451.)

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- Search for the term 'intent'
- Methods Statistical Analysis
 - Analyses were performed in the intention-to-treat population, defined as all patients who underwent randomization except those who did not provide consent, those for whom the family declined inclusion, and those who did not meet the inclusion criteria as defined in the protocol.

Evidence Synthesis Primer (Part 2)

Reviewer Name:	Answer Key		
Review Date:	05/21/2020		
PMID:	32160661 (Barrot)		
Journal Article Title:	Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress		
	Syndrome. (2020) Among patients with acute respiratory distress syndrome (ARDS) does		
Clinical Question:	Among patients with acute respiratory distress syndrome (ARUS) does conservative vs. liberal oxygen therapy improve all-cause mortality at 28 days.		
Clinical Question Type:	⊠ Treatment		
	Diagnosis		
	Prognosis		
	Systematic Review/Meta-Analysis		
Study Decige:			
Study Design:	Prospective, randomized open label study.		
Sample Size and Power:	850 patients 90% between group a priori power analysis based on an expected effect		
	size of 9% from published results of two prospective trials		
	396 were eligible, 191 were excluded: 205 randomized		
	Trial stopped by the DSMB for increased adverse risk in the conservative		
	oxygenation group.		
Validity Assessment:	Criteria	Assessment	
	Randomization	Computer randomization stratified by center, age, and severity of respiratory failure	
	Blinding	Open Label (not blinded based on impossibility of making treatment assignment)	
	Baseline Group	Groups were comparable based on review of	
	Comparability	Table 1	
	Follow up	Survival curves indicate patients were followed up to 90 days after surgery. Four patients our of 205 randomized were excluded from analysis (2%).	
	Intent to Treat	Analyses were performed in the intention to treat population, defined as all patients who underwent randomization minus exclusions.	
Validity Summary:	After examining randomization, baseline group comparability, follow up		
valaty contrary.	and intent to treat, this study was determined valid for informing		
	practice. While the study was not blinded, the open label nature of this		
	experiment did not likely change study outcomes.		

- Sample Size and Power
- Randomization
- Blinding
- Baseline Group Comparability
- Follow-Up
- Intent to Treat



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Questions?



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Thank You!

Open for Questions



Feedback Survey

A link to the feedback survey has been sent to the email address you used to register.

Please get out your device, find that email, and spend a few moments completing that survey before you leave today.

Tip: If on a mobile device, shift view to landscape view (sideways) for better user experience.