

MetaAnalysis – Systematic Review Potential PURL Review Form PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL [to be completed by PURLs Project Manager]

- A. Citation: Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet*. 2018 Apr 28;391(10131):1693-1705. doi: 10.1016/S0140-6736(18)30479-3. Epub 2018 Apr 26. Review. PubMed PMID: 29726345.
- B. Link to PubMed Abstract: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29726345>
- C. First date published study available to readers: 4/26/2018
- D. PubMed ID: 29726345
- E. Nominated By: Jim Stevermer
- F. Institutional Affiliation of Nominator: University of Missouri
- G. Date Nominated: 5/13/2018
- H. Identified Through: The Lancet
- I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
- J. Nomination Decision Date: 5/16/2018
- K. Potential PURL Review Form (PPRF) Type: Systematic Review
- L. Assigned Potential PURL Reviewer: Bob Marshall
- M. Reviewer Affiliation: Madigan Army Medical Center
- N. Abstract: BACKGROUND:
Supplemental oxygen is often administered liberally to acutely ill adults, but the credibility of the evidence for this practice is unclear. We systematically reviewed the efficacy and safety of liberal versus conservative oxygen therapy in acutely ill adults.

METHODS:

In the Improving Oxygen Therapy in Acute-illness (IOTA) systematic review and meta-analysis, we searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, HealthSTAR, LILACS, PapersFirst, and the WHO International Clinical Trials Registry from inception to Oct 25, 2017, for randomised controlled trials comparing liberal and conservative oxygen therapy in acutely ill adults (aged ≥ 18 years). Studies limited to patients with chronic respiratory diseases or psychiatric disease, patients on extracorporeal life support, or patients treated with hyperbaric oxygen therapy or elective surgery were excluded. We screened studies and extracted summary estimates independently and in duplicate. We also extracted individual patient-level data from survival curves. The main outcomes were mortality (in-hospital, at 30 days, and at longest follow-up) and morbidity (disability at longest follow-up, risk of hospital-acquired pneumonia, any hospital-acquired infection, and length of hospital stay) assessed by random-effects meta-analyses. We assessed quality of evidence using the grading of recommendations assessment, development, and evaluation approach. This study is registered with PROSPERO, number CRD42017065697.

FINDINGS:

25 randomised controlled trials enrolled 16 037 patients with sepsis, critical illness, stroke, trauma, myocardial infarction, or cardiac arrest, and patients who had emergency surgery. Compared with a conservative oxygen strategy, a liberal oxygen strategy (median baseline saturation of peripheral oxygen [SpO₂] across trials, 96% [range 94-99%, IQR 96-98]) increased mortality in-hospital (relative risk [RR] 1.21, 95% CI 1.03-1.43, I²=0%, high quality), at 30 days (RR 1.14, 95% CI 1.01-1.29, I²=0%, high quality), and at longest follow-up (RR 1.10, 95% CI 1.00-1.20, I²=0%, high quality). Morbidity outcomes were similar between groups. Findings were robust to trial sequential, subgroup, and sensitivity analyses.

INTERPRETATION:

In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO₂ range of 94-96%. These results support the conservative administration of oxygen therapy.

O. Pending PURL Review Date: 1/2/2019

SECTION 2: Critical Appraisal of Validity **[to be completed by the Potential PURL Reviewer]**

- A. What types of studies are included in this review?
The study is a meta-analysis of randomized controlled trials.
- B. What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses.
The key question addressed is evaluating all-cause mortality related to liberal versus conservative oxygen therapy in the acutely ill adult. Based on rigorous analysis to minimize potential biases, the study concluded that there is an increased risk of mortality with liberal use of oxygen.
- C. Study addresses an appropriate and clearly focused question. Well covered
Comments:
- D. A description of the methodology used is included. Well covered
Comments:
- E. The literature is sufficiently rigorous to identify all the relevant studies. Well covered
Comments:
- F. Study quality is assessed and taken into account. Well covered
Comments:
- G. There are enough similarities between selected studies to make combining them reasonable.
Well covered
Comments:
- H. Are patient oriented outcomes included? If yes, what are they?
Yes. Mortality and morbidity related to liberal vs conservative oxygen therapy.

- I. Are adverse effects addressed? If so, how would they affect recommendations?
Yes—these were the primary and secondary outcomes of the study.
- J. Is funding a potential source of bias? If yes, what measures (if any) were taken to ensure scientific integrity?
No.
- K. To which patients might the findings apply? Include patients in the metaanalysis and other patients to whom the findings may be generalized.
Acutely ill adults. Studies that included patients <18 years of age, pregnant patients, patients with chronic respiratory diseases, psychiatric diseases, patients on extracorporeal life support and patients treated with hyperbaric oxygen therapy were excluded. In addition, patients presenting for elective surgery were excluded. Results may not be generalizable to the excluded populations.
- L. In what care settings might the findings apply, or not apply?
Results apply to any care setting that manages acutely ill adults.
- M. To which clinicians or policy makers might the findings be relevant?
Findings are relevant to all clinicians and policy makers who manage acutely ill adults in the inpatient or pre-hospitalization setting.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions: For up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: <http://www.uptodate.com>. {Insert date modified if given.} Accessed February 12, 2009. [whatever date PPRF reviewer did their search.]

For DynaMed, use the following style:
 Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at <http://www.DynamicMedical.com>. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts

Hypoxemia: Approach to the patient {supplemental oxygen acutely ill}

Management Considerations:

- emergency management may require cardiopulmonary resuscitation and emergency oxygen therapy prior to hospital arrival

- supplemental oxygen therapy recommended for all acutely hypoxemic patients and patients at risk of hypoxemia management (including target oxygen saturation) varies based on risk of hypercapnic respiratory failure and underlying etiology

- liberal oxygen therapy may increase mortality compared to conservative oxygen therapy in acutely ill adults (level 2 [mid-level] evidence)

- high-flow oxygen therapy (50 L/minute) through nasal cannula may not reduce 28-day intubation rate but appears to reduce 90-day mortality compared to standard oxygen therapy or noninvasive ventilation in patients with non-hypercapnic acute hypoxemic respiratory failure (level 2 [mid-level] evidence) (see also High-flow nasal cannula oxygen in adults)

-clinical risks of supplemental oxygen include worsening of hypercapnic respiratory failure, delayed recognition of clinical deterioration, and oxygen toxicity to retina and lung when high fractions of inspired oxygen are used

B. DynaMed citation/ Title. Author. In: DynaMed [database online]. Available at: access date www.DynamicMedical.com Last Updated: . Accessed

Hypoxemia: approach to the patient {supplemental oxygen acutely ill}. In: DynaMed [database online]. Available from <http://www.dynamed.com/login.aspx?direct=true&site=DynaMed&id=920488>. Last updated 2017 Sep 01. Accessed 28 December, 2018.

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

Liberal oxygen therapy may increase mortality compared to conservative oxygen therapy in acutely ill adults. Supplemental oxygen therapy should be considered for hypoxemic patients or those at risk of hypoxemia.

D. UpToDate excerpts

Metabolic demand is elevated in critically ill patients (eg, acute respiratory distress syndrome, sepsis, or septic shock). VO_2 increases because more oxygen is required to maintain aerobic cellular metabolism. In critically ill patients, VO_2 elevation may be disproportionately accomplished by increasing the delivery of O_2 (DO_2). This is different from healthy individuals in whom VO_2 elevation is disproportionately accomplished by increasing the oxygen extraction, with DO_2 contributing little. Whether such a difference exists between healthy and critically ill individuals is controversial:

- Proponents believe that VO_2 is disproportionately affected by DO_2 because oxygen extraction is impaired during critical illness. Supporting this hypothesis, lactic acidosis is often present despite increased DO_2 . In other words, anaerobic metabolism is required despite an increased supply of oxygen. Ineffective oxygen extraction may be due to poor oxygen uptake or poor utilization by the cells.

- Opponents argue that both VO_2 and DO_2 were calculated in most of the studies that suggest that DO_2 has a disproportionate impact on VO_2 during critical illness. This could introduce mathematical coupling errors, which would falsely increase the strength of the relationship

between VO₂ and DO₂. In addition, VO₂ was not disproportionately affected by DO₂ in the few studies that directly measured VO₂.

We believe that the relationship between DO₂ and VO₂ in critically ill patients is similar to that in healthy patients during increased metabolic demand (eg, exercise, pregnancy). In other words, we believe that increased oxygen extraction, and not increased DO₂, has the greatest impact on increasing the VO₂ in critically ill patients. We base this belief on the following:

- Numerous studies have evaluated the impact of augmenting DO₂ on VO₂ with conflicting results. Methods of augmenting DO₂ have included inotropic agents, saline loading, and vasodilators to improve cardiac output, as well as red blood cell transfusions to increase arterial oxygen content (CaO₂). Regardless of the intervention, DO₂ and VO₂ were strongly correlated when VO₂ and DO₂ were both calculated, but not when VO₂ was directly measured.
- A few studies have evaluated the impact of augmenting DO₂ and patient-centered outcomes, such as survival, organ failure, length of ICU stay, and length of hospitalization [35,37-39,45-51]. While some of the studies found an improvement in morbidity or mortality, others found no effect or potential harm. Those that demonstrated improvement had significant methodologic problems, such as baseline differences between the treatment and control groups, and failure to use an intention-to-treat analysis.

Taken together, we believe there are insufficient data to warrant the routine augmentation of DO₂ in critically ill patients if there is no evidence of ongoing tissue hypoxia.

E. UpToDate citation

Rosen IM, Manaker S. Oxygen delivery and consumption. In: Basow DS, ed. UpToDate [database online]. Available at: <http://www.uptodate.com>. Last updated: 12 June 2017. Accessed 2 January 2019.

Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

In critically ill patients in whom there is no evidence of ongoing tissue hypoxia, we suggest that DO₂ should NOT be routinely augmented (Grade 2B).

F. Other excerpts (USPSTF; other guidelines; etc.):

British Thoracic Society Guidelines

1 Assessing patients

- For critically ill patients, high-concentration oxygen should be administered immediately and this should be recorded afterwards in the patient's health record.

- Clinicians must bear in mind that supplemental oxygen is given to improve oxygenation but it does not treat the underlying causes of hypoxemia which must be diagnosed and treated as a matter of urgency.

- The oxygen saturation should be checked by pulse oximetry in all breathless and acutely ill patients, ‘the fifth vital sign’ (supplemented by blood gases when necessary) and the inspired oxygen concentration should be recorded on the observation chart with the oximetry result. (The other vital signs are pulse rate, blood pressure, temperature and respiratory rate).

- Pulse oximetry must be available in all locations where emergency oxygen is used. Clinical assessment is recommended if the saturation falls by $\geq 3\%$ or below the target range for the patient.

- All critically ill patients outside of a critical care area (e.g., intensive care unit (ICU), high dependency unit (HDU), respiratory HDU) should be assessed and monitored using a recognized physiological track and trigger system such as the National Early Warning Score (NEWS).

Target oxygen prescription:

- Oxygen should be prescribed to achieve a target saturation of 94–98% for most acutely ill patients or 88–92% or patient-specific target range for those at risk of hypercapnic respiratory failure.

G. Citations for other excerpts

O'Driscoll BR, Howard LS, Earis J on behalf of the British Thoracic Society Emergency Oxygen Guideline Group, et al. BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax 2017;72:ii1-ii90.

H. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

For critically ill patients, high-concentration oxygen should be administered to achieve a target saturation of 94-98%.

SECTION 4: Conclusions

[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer as needed]

- A. **Validity:** Are the findings scientifically valid? Yes
- B. If **A** was coded “Other, explain or No”, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?
- C. **Relevance:** Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?
Yes
- D. If **C** was coded “Other, explain or No”, please provide an explanation.

E. **Practice changing potential:** If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?

Yes

F. If E was coded as “Yes”, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

The study implies that given an increased mortality benefit with liberal oxygen therapy, an FiO₂ range with an upper limit should be implemented for treatment of the acutely ill adult. Implementation of such a guideline/policy would help reduce mortality.

G. **Applicability to a Family Medical Care Setting:**

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? Yes

H. Please explain your answer to G.

After the guideline/policy is validated, it could easily be implemented by the family physician treating acutely ill adults. Education about the new policy will be important initially for widespread implementation.

I. **Immediacy of Implementation:**

Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? Yes

J. If I was coded “Other, explain or No”, please explain why.

Immediate implementation is feasible as soon as an updated guideline is established.

K. **Clinically meaningful outcomes or patient oriented outcomes:**

Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?

Yes

L. If K was coded “Other, explain or No”, please explain why.

M. In your opinion, is this a pending PURL? Yes

1. Valid: Strong internal scientific validity; the findings appear to be true.

2. Relevant: Relevant to the practice of family medicine.
3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
4. Applicability in medical setting.
5. Immediacy of implementation

N. Comments on your response for question M.

N/A