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Critical Care [ALERT]

Authoritative, evidence-based summaries for the critical care clinician

SPECIAL FEATURE

Sepsis Guidelines Revisited

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Dr. McFeely reports no financial relationships relevant to this field of study.

The Surviving Sepsis Campaign recently published a revised *International Guidelines for the Management of Severe Sepsis and Septic Shock*, updating its 2008 guidelines.[1] A consensus committee of 68 experts, representing 30 international organizations, participated. Committee proceedings were conducted independently with no industry funding and were regulated by a formal conflict of interest policy. The 58-page document makes recommendations in three large categories: treatment of severe sepsis, general care of critically ill patients, and pediatric considerations. The authors follow the principles of Grading of Recommendations of Assessment Development Evaluation (GRADE)[2] to determine quality of evidence from high (A) to very low (D) and strength of recommendation as strong (1) or weak (2).

In accordance with the GRADE system, the guidelines place greater emphasis on strength of recommendation than quality of evidence. Strong recommendations are described as "we recommend" and weak recommendations as "we suggest." The authors include literature available through the fall of 2012. Specific recommendations mentioned in this special feature are followed by their GRADE recommendation in parenthesis. The definitions of suspected sepsis, severe sepsis, and septic shock are based on consensus conference recommendations.[3]

INITIAL RESUSCITATION

Initial resuscitation of severe sepsis continues to follow the early goal-directed therapy (EGDT) guidelines, including a central venous pressure (CVP) of 8-12 mmHg, mean arterial pressure (MAP) of ≥ 65 mmHg, urinary output > 0.5 mL/kg/hr, and either superior vena cava oxygenation saturation ($ScvO_2$) or mixed venous oxygen saturation (SvO_2) of 70% or 65%, respectively (*see Table 1*).[4] When sepsis is suspected, a new

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Table 1. Surviving Sepsis Campaign Bundles	
Timing	**Measures to be completed**
In first 3 hours	Crystalloid infusion, 30 mL/kg
	Measurement of serum lactate
	Appropriate cultures obtained, followed by administration of antibiotics
In first 6 hours	Vasopressors to keep mean arterial pressure > 65 mmHg
	If lactate > 4 mmol/L, or pressors needed:
	• Measurement of central venous pressure
	• Measurement of central venous oxygen saturation (SvO_2)
	Monitoring of serum lactate if initial value abnormal
Adapted from Dellinger RP, et al[1] and Rivers E, et al.[4]	

3-hour bundle is recommended, including checking serum lactate level, obtaining blood cultures, administrating antibiotics, and giving 30 mL/kg crystalloid (increased from 20 mL/kg in the 2008 guidelines) for hypotension or lactate > 4 mmol/L. The 6-hour EGDT window includes administering vasopressors for hypotension not responding to fluids and measuring CVP and SvO_2 in the event of persistent arterial hypotension despite volume resuscitation or a lactate > 4 mmol/L. Lactic acid levels should be followed.

HEMODYNAMIC SUPPORT

Crystalloids are the recommended fluid for the initial resuscitation of severe sepsis and septic shock (1B). Hydroxyethyl starches are not recommended (1B).[5] Albumin is suggested for fluid resuscitation when patients require substantial amounts of crystalloid (2C).

Vasopressors (*see Table 2*) should be initiated to maintain a mean arterial pressure of 65 (1C). Norepinephrine is the first choice of vasopressor (1B).[6] Epinephrine, added to and potentially substituted for norepinephrine, is the second agent recommended for use as needed to maintain an adequate MAP (2B). Vasopressin may be added to epinephrine either to raise MAP or to decrease norepinephrine dosage. Dopamine is not recommended except in highly selected patients who may have a low risk of tachyarrhythmia and/or have significant bradycardia. Phenylephrine is also not recommended except where norepinephrine has caused arrhythmias, when cardiac output is high, or as salvage therapy when combined with low-dose vasopressin (1C).

Dobutamine may be administered or added to vasopressors in the presence of myocardial dysfunction as suggested by high cardiac filling pressures and low cardiac output or ongoing signs of hypoperfusion, despite adequate intravascular volume and mean arterial pressure (1C).

STEROIDS

Corticosteroids are not recommended to treat adult septic shock if fluids and vasopressor therapy alone are able to restore hemodynamic stability. If this is not achievable, then intravenous hydrocortisone at a dose of 200 mg per day is suggested (2C). Adrenocorticotropin stimulation tests are discouraged. Steroids should be

Table 2. Vasopressors

- Target mean arterial pressure (MAP) at least 65 mmHg (1C)
- Norepinephrine (NE) first choice as agent (1B)
- Epinephrine second choice pressor (2B)
- Vasopressin (0.03 u/min) may be added to NE to decrease NE dose or raise MAP (ungraded)
- Phenylephrine not recommended except as salvage, when NE causes arrhythmias, or known high cardiac output state (1C)
- Dobutamine trial if myocardial dysfunction suggested, or ongoing hypotension after volume resuscitation (1C)

Table 3. Pediatric Resuscitation	
Similar definitions of sepsis and organ dysfunction to adult recommendations	
0 min	Recognize altered level of consciousness and/or hypoperfusion
5 min	Start intravenous or intraosseous crystalloid bolus up to 60 mL/kg unless dyspnea or liver distention present
15 min	Fluid refractory shock: begin pressors (intravenous or intraosseous)
	• Dopamine for "cold shock"
	• Norepinephrine for "warm shock"
60 min	Admission to pediatric ICU
	If refractory shock:
	• Hydrocortisone
	• Monitor CVP and SVO_2 (same goals as for adults)
	Persistent shock
	• Rule out pneumothorax, pericardial disease, and/or abdominal compartment syndrome
	• Consider extracorporeal membrane oxygenation
Per new guidelines,[1] based on recommendations of the American College of Critical Care Medicine (1C)[10,11]	

tapered when pressors are no longer required and should not be administered for the treatment of sepsis in the absence of shock (1D). It is further suggested that hydrocortisone be given as a continuous infusion (2D).

SUPPORTIVE THERAPIES

Supportive therapies for severe sepsis are also discussed. As before, transfusion of packed red blood cells is recommended as part of EGDT. Once tissue hypoperfusion has resolved, the transfusion trigger decreases to a hemoglobin level of < 7 gm/dL (1B). Erythropoietin is not recommended as treatment for anemia associated with sepsis (1B). The guidelines suggest that fresh frozen plasma not be used to correct clotting abnormalities in the absence of bleeding or invasive procedures (2D). Antithrombin is not recommended (1B); and neither intravenous immunoglobulin (2B) nor intravenous selenium (2C) is suggested. The use of recombinant activated protein C (drotrecogin alpha; Xigris®) has been removed from the guidelines.

Tight gylcemic control has also been removed, in favor of a targeted upper blood glucose < 180 mg/dL(1A).[7] Renal replacement therapy and management of ventilator bundles, nutrition, and goals of care are also discussed, with recommendations consistent with guidelines published elsewhere for those specific components of overall critical care.[8,9] A large section of the guidelines focuses on the treatment of pediatric sepsis. These guidelines follow recommendations from the American College of Critical Care Medicine (*see Table 3*).[10,11]

CONCLUSION

This publication is a timely and unbiased update in an important clinical area. The authors point out that the guidelines are not standards of care: Specific recommendations for individual patients must be individualized based on clinical criteria. The guidelines do an excellent job of collating all relevant recommendations and synthesizing the literature related to each point of discussion. Every hospital should adopt this document as its starting point for reassessing local management of sepsis. ■

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ABSTRACT & COMMENTARY

Early Tracheotomy is Not Associated with Improved Mortality and Morbidity

By Betty Tran, MD, MS

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Dr. Tran reports no financial relationships relevant to this field of study.

SYNOPSIS: This multicenter, randomized trial of university and non-university ICUs in the United Kingdom found that tracheotomy within 4 days of critical care admission compared to late tracheotomy (≥ 10 days) was not associated with an improvement in 30-day, 1-year, or 2-year mortality, length of ICU stay, or antibiotic-free days.

SOURCE: Young D, et al. Effect of early vs. late tracheostomy placement on survival in patients receiving mechanical ventilation: The TracMan randomized trial. *JAMA* 2013;309:2121-2129.

The Tracheostomy Management (TracMan) study enrolled adult patients receiving mechanical ventilation in 70 general and two cardiothoracic surgical ICUs from both university and non-university hospitals across the United Kingdom between 2004 and 2008 who were deemed by their treating physicians within the first 4 days of admission to be likely to require at least 7 more days of ventilatory support. Of the 1032 eligible patients, 909 were ultimately randomized 1:1 to receive early tracheotomy (within 4 days of randomization) or late tracheotomy (after 10 days, if still clinically indicated). The primary outcome was all-cause 30-day mortality, with secondary outcome measures being mortality at ICU discharge, 1 and 2 years, ICU and acute hospital length of stay, number of days receiving sedatives, and antimicrobial-free days.

There was no significant difference in 30-day mortality between the early vs late tracheotomy group (absolute risk reduction 0.7; 95% confidence interval, -5.4-6.7, $P = 0.89$). ICU and acute-hospital lengths of stay and 1- and 2-year survival rates were also similar between the two groups. Median duration of ICU admission was similar at 13.0 (IQR 8.2-19.1) days in the early group compared to 13.1 (IQR 7.4-23.6) days in the late group ($P = 0.74$), with comparable median total hospital length of stay (33 vs 34 days, respectively, $P = 0.68$). In patients who survived to 30 days after randomization, there was a significant difference in the number of days sedatives were given in the early tracheotomy group (5 days, IQR 3-9) vs the late group (8 days, IQR 4-12; $P < 0.001$), but no difference in sedative use when patients not surviving to 30 days were compared and no overall difference in antibiotic use.

Notably, in the late tracheotomy group, only 45% of patients ultimately underwent the procedure. In more than two-thirds of the rest, a tracheotomy was no longer clinically indicated because the patient had recovered with no further mechanical ventilatory needs or had been discharged alive from the ICU. Interestingly, the investigators attempted but were unable to generate a validated and accurate prediction tool that could help determine the duration of mechanical ventilation for an individual patient. However, when compared to other studies with published predictive "rules," the rate at which patients recovered before tracheotomy remained similar at approximately 20%, suggesting that any rules used were no better than clinical judgment.

■ COMMENTARY

Although this study lost some power when it did not reach its target sample enrollment (the authors originally planned for 1208 patients, then revised it to 1692, and ended up with a final sample of 899), it remains the largest randomized trial to date and is probably the best data we currently have in the debate between early vs late tracheotomy. As the authors point out, this question is critical in the United Kingdom given the pressures to pursue early tracheotomy due to limited ICU beds and increased severity of

illness among patients admitted to the ICU; they quote one U.K. survey that revealed half of all tracheotomies were performed within 1 week of ICU admission.

Not only was there no survival advantage or other significant length of stay benefits to early tracheotomy compared to a late "watchful waiting" policy, but the observation that only 45% of patients in the late group ultimately underwent tracheostomy placement mainly due to successful extubation and subsequent ICU discharge suggests that an early strategy will lead to a large number of unnecessary tracheotomies with inherent procedure risks. Although the tracheotomy complication rate in the study was relatively low at 6.3%, this may not be generalizable to other centers as the vast majority of tracheotomies performed in these cases were percutaneous, dilator-based ones done at bedside. In addition, this observation highlights our current inability to predict accurately who will need prolonged mechanical ventilation. One can argue, however, that robust prediction tools may not be vital as based on the study findings, delaying decisions about tracheotomy until at least day 10 was not associated with any significant increase in morbidity or mortality.

■ EDITOR'S COMMENTARY
DAVID J. PIERSON, MD

This study brings us a bit closer to resolving a longstanding and hotly debated issue in ICU management: when and why to perform a tracheotomy on a mechanically ventilated patient with acute respiratory failure. Nearly two decades ago, during *Critical Care Alert's* first year of publication, Leslie Hoffman wrote a special feature summarizing the pros and cons of early vs late tracheotomy, primarily from the perspective of complications.[1] Since then, bedside percutaneous dilational tracheotomy has made the procedure accessible to non-surgical intensivists and become standard of care in many centers. In addition, noninvasive ventilation has expanded the options for full- or part-time ventilatory support for some patients who need this long term. However, when and why to do a tracheotomy remain common and contentious questions in the management of many critically ill patients.

There are two main reasons why this issue remains problematic after 40 years. The first is the lack of an effective means for identifying up-front which patients will need prolonged ventilatory support.[2] Many studies have attempted to devise criteria that could be applied within a day or two of intubation to predict subsequent weaning failure and the continued need for invasive mechanical ventilation two or more weeks later. As in the present study, such predictive criteria have invariably identified many patients as needing prolonged ventilation who are in fact extubated successfully during the next week or two. Except for a few highly specific circumstances (such as in some high cervical spinal cord injuries), performing tracheotomies within the first few days of intubation will invariably mean doing this procedure on some patients who do not actually need it.

The second reason is the absence of equipoise among intensivists with respect to the timing of tracheotomy, including researchers who attempt to study it.[2] In order for a randomized clinical trial to succeed, investigators must agree to apply both study arms, and patients have to be allotted equally to the two treatments being evaluated. With respect to when patients should undergo tracheotomy, despite the absence of definitive scientific evidence, every practitioner and potential investigator seems to feel strongly enough about one or the other of the options to be bothered ethically by the idea of randomizing half their patients to receive the other option. The result in nearly all previous studies has been disrupted randomization, protocol violations, and/or failure to enroll sufficient patients, such that the primary research question cannot be answered definitively. As indicated above by Dr. Tran, the present study by Young and colleagues helps to resolve the dilemma with its finding that waiting at least 10 days to decide whether to do a tracheotomy, if the patient still requires airway access and ventilatory support at that point, does not seem to be harmful.

The three most compelling reasons for tracheotomy in a patient with acute respiratory failure remain: 1) facilitation of airway clearance; 2) airway access for long-term mechanical ventilation when noninvasive ventilation is not an option; and 3) facilitation of communication in patients who are awake, alert, and capable of speaking. For patients in whom one or more of these conditions exist, most intensivists consider tracheotomy when it appears after 1-3 weeks that extubation will not be successful or safe in the near future. A caveat, however, is that we have learned from many studies on weaning that liberation from ventilatory support cannot be predicted with certainty without (usually several) empirical trials of spontaneous breathing. ■

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ABSTRACT & COMMENTARY

Effects of Standardizing Procedures on Adverse Effects of Endotracheal Suctioning

By David J. Pierson, MD, Editor

SYNOPSIS: This study shows that adverse effects of endotracheal suctioning, particularly oxygen desaturation and hemorrhagic secretions, are frequent in mechanically ventilated patients, and can be reduced by the implementation of practice guidelines.

SOURCE: Maggiore SM, et al. Decreasing adverse effects of endotracheal suctioning during mechanical ventilation by changing practice. *Respir Care* 2013; Mar 6. [Epub ahead of print].

Maggiore and colleagues studied the incidence of adverse effects of endotracheal suctioning in a 26-bed French medical ICU, and assessed the impact on this incidence of implementing a new set of institutional guidelines related to suctioning practices. They used a before-and-after study design, first prospectively documenting *a priori* defined suctioning-related events and complications on 79 intubated, ventilated patients (4506 suctioning procedures) during a 3-month period when there were no specific suctioning guidelines in the unit, and then repeating the observations 1 year later, after guideline implementation, in 68 patients (4994 procedures). The suctioning guidelines used were similar to those of the American Association for Respiratory Care (AARC),[1] but were developed independently, shortly before the latter were published.

Suctioning-associated adverse events were frequent prior to guideline implementation, occurring at least once in 60% of the patients. Most frequent among these were oxygen desaturation (SpO_2 decrease of ≥ 5%; occurring during 6.5% of all suctioning procedures and in 47% of patients) and hemorrhagic secretions (in 4% of procedures and 32% of patients). Severe hypertension (systolic BP > 200 mmHg) occurred in 14 patients (18%), hypotension (BP < 80 mmHg) in seven (9%), tachycardia (rate > 150/min) in five (6%), and bradycardia (rate < 50/min) in four (5%); one patient experienced transient, spontaneously resolving ventricular tachycardia during suctioning.

During the second observation period, after implementation of the suctioning guidelines, adverse events were less frequent (in 5% vs 12% of all procedures, $P < 0.05$) and occurred in only 43% of the patients. Each adverse event the investigators evaluated was significantly reduced during the post-guideline period. Considering both periods together, receiving positive end-expiratory pressure > 5 cm H_2O was an independent risk factor for desaturation, and being suctioned > 6 times/day was associated with both desaturation and hemorrhagic secretions. The authors conclude that endotracheal suctioning frequently induces adverse events, and that carrying out the procedure according to current guidelines reduces their incidence.

■ COMMENTARY

Endotracheal suctioning in critically ill patients receiving mechanical ventilation can induce potentially life-threatening adverse events such as desaturation, bleeding into the airways, hemodynamic instability, and arrhythmias. This study corroborates this long-recognized fact, and more importantly, reminds us that the incidence and severity of suctioning-related adverse events can be reduced if current best practices are followed during the procedure.

Prior to implementation of the practice guideline in the authors' ICU, intubated patients were suctioned routinely at least every 2 hours, and disconnected from the ventilator circuit for the procedure (closed suction systems generally not being used). Saline was frequently instilled; high suction pressures (400 cm H_2O or more) were often used; and the duration of suctioning, the size of the catheter, and its depth of insertion were not standardized. The new suctioning protocol, essentially congruent with the AARC guidelines,[1] was implemented between the study's two observation periods using multi-modality educational procedures targeted at all ICU staff.

Along with other items, the new guideline included the following changes:

- Avoidance of circuit breaks, generally via use of closed-system catheter sets;
- Sterile technique at all times;
- No routine suctioning: as-needed only (except for paralyzed patients);
- Avoidance of saline instillation;
- Use of catheter of appropriate size for internal diameter of artificial airway;
- Limiting duration of suction application and

suction pressure used; and,
- Avoiding passing the catheter too far down the airway.

Endotracheal suctioning is a necessary part of the respiratory care of critically ill patients. Although no mortality or lasting morbidity were observed in the study by Maggiore et al, that such outcomes can be associated with suctioning procedures is without question to anyone who has worked long-term in the ICU. Although the strength of the evidence supporting each of the above protocol elements varies, the measures listed constitute current best practice based on what is known. Their use in all intubated patients can be expected to reduce the incidence and severity of suctioning-associated adverse events to the lowest levels currently attainable. ■

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ABSTRACT & COMMENTARY

Prone Positioning and the Emerging Paradigm for Managing Severe ARDS

By Richard H. Kallet, MS, RRT, FAARC, FCCM

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Mr. Kallet reports no financial relationships relevant to this field of study.

SYNOPSIS: In this prospective, multicenter, randomized, controlled trial, 466 patients with severe acute respiratory distress syndrome were managed with protocolized lung-protective ventilation, with either supine positioning or prone positioning for at least 16 hours/day. Both 28-day and 90-day mortality were significantly reduced in those managed with prone positioning.

SOURCE: Guérin C, et al for the PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159-2168.

The study was conducted in 26 ICUs that had at least 5 years' experience with prone positioning (PP). Only patients with acute respiratory distress syndrome (ARDS) and a sustained (12-24 hours) arterial oxygen tension-to-inspired oxygen fraction (PaO_2/FiO_2) ratio < 150 mmHg after enrollment were eligible for randomization. Ventilator management similar to the original ARDS Net protocol was applied in both treatment arms. Also, protocols for paralytics, sedation, inhaled nitric oxide, and other measures were used. At study entry, there were no differences in ventilator settings or arterial blood gas values. Likewise, baseline demographic and physiologic profiles of the patients were similar. However, there were statistically significant increases in Sepsis-related Organ Failure Assessment (SOFA) scores and vasopressor use in the supine group, and more use of paralytics in the PP group.

Both 28- and 90-day mortality were reduced in the PP vs supine positioning groups (16.0 vs 32.8%, and 23.6 vs 41%, respectively; $P < 0.001$), differences that remained significant even after adjustment for both SOFA score and paralytics. There also was a trend toward higher use of rescue therapies in the supine group. Patients in the PP arm had a greater number of ventilator-free days at 28 and 90 days compared to the supine arm (14 ± 9 vs 10 ± 10 and 57 ± 34 vs 43 ± 38; $P < 0.001$, respectively). Likewise, the proportion of patients successfully extubated by day 90 was higher in the PP group (80.5%) vs the supine group (65%; $P < 0.001$).

■ COMMENTARY

The PROSEVA study confirms a recent meta-analysis of seven randomized, controlled trials (RCTs) that found a survival benefit with the use of PP only in ARDS patients whose PaO_2/FiO_2 ratio was < 100 mmHg (relative risk, 0.84; 95% confidence interval, 0.74-0.96; $P = 0.01$, n = 555).[1] Previous RCTs enrolled patients with varying severity of ARDS, sometimes limited the exposure to PP to 7-9 hours per day, and did not always include lung-protective ventilation in all patients. In contrast, the PROSEVA study design was admirable both in its attempt to exclude patients who recovered rapidly and in its incorporation of protocols to control for other potential confounders.

PP favorably alters the pulmonary hydrostatic pressure gradient, thus increasing trans-pulmonary pressure within dorsal lung regions. This accentuates the relative effect of applied airway pressure (both driving pressure and PEEP), so that relatively higher proportions of both tidal ventilation and end-expiratory volume are

preferentially redistributed to these areas. Alterations in gravitational forces also reduce the compressive effects of the mediastinum on lung tissue. In effect, PP in ARDS functions as a recruitment maneuver. Moreover, as less pulmonary vasculature is oriented toward the ventral lungs, blood flow resistance remains lower in the dorsal regions so that pulmonary perfusion remains relatively intact. Therefore, overall ventilation-perfusion matching, and thus oxygenation, typically improve.

That PP promotes lung-protective ventilation likely explains the improved survival in severe ARDS. Functional residual capacity (FRC) is a key determinant of oxygenation. It also affects pulmonary elastic recoil properties, and therefore determines the strain-stress relationships believed responsible for ventilator-induced lung injury. By returning FRC toward normal (through recruitment of collapsed alveoli), both shear injury and excessive regional strains and stresses are reduced. In addition, improvements in oxygenation may reduce exposure to potentially toxic oxygen levels (e.g., $FiO_2 \geq 0.80$). Therefore, a mortality benefit associated with PP would more likely be manifested in severe ARDS, in which FRC and lung compliance are highly abnormal and patients must endure prolonged exposure to high strains-stresses and high FiO_2 that exacerbate lung inflammation.

The current study is consistent with a recent meta-analysis suggesting a survival benefit from high-PEEP only in those with more severe ARDS.[2] An emerging picture is that *early* intervention with low tidal volume ventilation, restoring FRC, and a period of complete control over the ventilatory pattern with paralytics[3] reduces mortality in ARDS. With severe infection or trauma, the body's inflammatory response is hyperstimulated. In these situations, therapies that exacerbate inflammation further may be overwhelming. Nonetheless, accumulating evidence from well-executed RCTs may now provide us with a more complete, evidence-based model to effectively treat severe ARDS. ■

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CME/CNE Questions

1. The first choice pressor for septic shock is:

a. dopamine.
b. norepinephrine.
c. phenylephrine.
d. epinephrine.

2. In the TracMan trial, compared to late tracheotomy (day 10 or later), early tracheotomy (within 4 days) was associated with:

a. no significant difference in 30-day mortality.
b. no significant difference in 2-year mortality.
c. no significant difference in ICU length of stay.
d. no significant difference in antibiotic-free days.
e. All of the above

3. In the study on adverse events during endotracheal suctioning, which of the following occurred after implementation of a best-practice guideline in the ICU?

a. Fewer patients in whom suctioning-associated adverse events occurred
b. Fewer instances of hemorrhagic airway secretions
c. Fewer cardiac arrests associated with suctioning
d. All of the above
e. a and b but not c

4. The potential benefits of prone positioning in patients with severe ARDS include all *except* which of the following?

a. Recruitment and better aeration of dorsal lung regions
b. Better ventilation:perfusion matching
c. Reduced shear injury
d. More homogenous strain/stress distribution throughout the lungs that reduces regional lung overinflation
e. Enhanced perfusion of ventral lung regions

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Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Our Newest Pharmacologic Class for Treatment of Diabetes: SGLT2 Inhibitors

Source: Polidori D, et al. *Diabetes Care* 2013;36:2154-2161.

The role of the kidney in glucose regulation has been underappreciated. Although perhaps counterintuitive, after persistent exposure to elevated glucose levels in the glomerular filtrate presented to the proximal renal tubule, the kidney adapts by reabsorbing *increased* amounts of glucose, thereby *increasing* blood sugar. The sodium glucose cotransporter (SGLT2) receptor is the primary pathway for renal tubular glucose reabsorption; blockade of this receptor results in enhanced urinary glucose excretion. Currently, the only FDA-approved agent for blockade of the SGLT2 receptor is canaglifozin.

In addition to potent SGLT2 receptor blockade, it has been suspected that canaglifozin might affect intestinal absorption of glucose by its modest inhibition of intestinal SGLT1. Polidori et al tested the impact of canagliflozin SGLT1 inhibition by examining the rate of gastrointestinal glucose absorption in healthy volunteers following a 600-kcal mixed-meal tolerance test.

Canagliflozin produced a very modest reduction in glucose absorption over a 6-hour interval (about 6%). The effects were accentuated in the early postprandial intervals, indicating a slowed absorption of glucose that was not attributable to delayed gastric emptying. Blunting of early postprandial glucose absorption should have a favorable effect on postprandial glucose excursions in diabetics.

Although enhanced urinary glucose excretion is the primary mechanism of plasma glucose lowering by SGLT2 inhibitors, modest gastrointestinal SGLT1 inhibition also appears to impact postprandial glucose excursion. ■

Bariatric Surgery vs Intensive Medical Therapy for Diabetes

Source: Kashyap SR, et al. *Diabetes Care* 2013;36:2175-2182.

The benefits of bariatric surgery (BAS) are increasingly recognized for obese patients with type 2 diabetes mellitus (T2DM). Indeed, the mechanisms by which diversionary surgery (e.g., gastric bypass) produces such prompt and dramatic remission in diabetic patients are still being elucidated. Long-term observational data on BAS for persons with severe obesity (body mass index [BMI] > 40) confirm durable weight reduction, improved control of diabetes, and even suggest reduced mortality.

Few trials have directly compared the efficacy of BAS with intensive medical treatment (IMT). Kashyap et al randomized T2DM subjects (n = 60) with moderate obesity (mean BMI = 36) to one of two BAS interventions (gastric sleeve or gastric bypass) or IMT in the Surgical Therapy And Medications Potentially Eradicate Diabetes (STAMPEDE) trial. Currently reported data include outcomes at 24 months.

In essentially every category assessed, BAS patients had superior outcomes to IMT. No BAS-related deaths occurred. At 2 years, degree of A1c control, LDL, HDL, total cholesterol, triglycerides, and CRP were all more improved in the BAS patients than in the IMT patients.

When comparing outcomes in the two BAS groups, even though weight loss was similar between gastric sleeve and bypass surgery, the latter achieved greater improvements in truncal fat reduction, leptin, insulin sensitivity, beta cell function, and incretin responses. BAS is more effective for multiple metabolic markers than IMT over the long term in T2DM patients. ■

Psoriasis and Risk for New Onset Diabetes

Source: Khalid U, et al. *Diabetes Care* 2013;36:2402-2407.

Inflammatory disorders like rheumatoid arthritis (RA) and psoriasis (PSOR) have recently been confirmed to be risk factors for adverse cardiovascular (CV) events, although the precise pathways through which such risk occurs remain controversial. Some have even gone so far as to say that RA should be considered an independent CV risk factor of equal potency to the already registered risk factors like hypertension, history of premature cardiovascular death, etc. Since PSOR and RA share common inflammatory pathways, it's perhaps not surprising that both are associated with CV adversity.

To date, the relationship between PSOR and diabetes mellitus (DM) has been controversial. Since DM is a major contributor to CV events, if PSOR and

DM are related, that would account for some of the increased CV risk.

Khalid et al report on an analysis of the PSOR-DM relationship discerned through a 12-year follow-up of Danish persons ≥ 10 years (n = 4,614,807). They studied the incidence of new-onset DM in PSOR subjects vs controls. A graded linear association between PSOR and new onset DM was found. Compared to the reference population, the incidence of DM in persons with mild PSOR was almost doubled, and in severe PSOR, nearly tripled. ■

Osteoporosis: Are Two Drugs Better Than One?

Source: Tsai JN, et al. *Lancet* 2013;382: 50-56.

Most women today who are receiving pharmacotherapy for treatment of osteoporosis receive oral bisphosphonates (e.g., alendronate, risedronate). Other effective treatments, like teriparatide (TERI) and denosumab (DENO) are usually reserved for more severe cases, in some part because they require parenteral administration.

Even though osteoporosis treatments have shown risk reduction for fracture and improved bone mineral density (BMD), restoration of full bone integrity remains a challenge. As one of the few anabolic tools (as opposed to anticatabolic tools like bisphosphonates), some investigators have tried to augment the favorable activity of TERI by combination with bisphosphonates, but the results have been disappointing. Whether the addition of DENO to TERI might be beneficial was the subject of investigation by Tsai et al. Postmenopausal women with osteoporosis (n = 100) were randomized to DENO, TERI, or both for 6 months. The primary outcome of the study was improvement in BMD.

Combination TERI+DENO appeared to be synergistic, with improvements in BMD greater than either agent alone and arithmetically greater than the anticipated benefit of combined monotherapies. For example, BMD increases at the hip were 4.2% for TERI+DENO, 0.8% for TERI, and 2.1% for DENO. These data support the consideration of TERI+DENO in highest-risk patients, those unable to take other treatments, or patients who fail to respond to other regimens. ■

Long-Term Impact of Weight Management on Blood Pressure

Source: Tyson CC, et al. *J Clin Hypertens* 2013;15:458-464.

The weight loss maintenance (WLM) trial randomized adults (n = 741) with hypertension (HTN) and/or dyslipidemia — but without evidence of cardiovascular disease — to one of several weight loss management programs. Although the initial outcome reports from WLM addressed the relative efficacies of different weight loss strategies over time, this report stratified study participants into those who lost, maintained, or gained weight over the 5-year study period. Tyson et al compared blood pressure effects between the three categories of weight impact, irrespective of which particular method of weight loss had been applied.

At study end, the weight-stable group had gained 0.6 kg, as compared with a 9.1 kg increase in the weight-gain group, and a 7.1 kg decrease in the weight-loss group. The weight-stable and the weight-gain groups were noted to have similar increases in systolic blood pressure (SBP) over 5 years (SBP increase mean 4.2 mmHg), whereas the weight-loss group SBP was not statistically significantly changed.

In contrast to some other trials that report a "legacy effect" (prolonged beneficial impact of early intervention, even after the intervention has ceased), initial weight loss in WLM was not associated with favorable SBP effects if weight was regained. On the other hand, sustained modest weight reduction (< 10% of baseline BMI) had a sustained effect to maintain SBP. Although simply maintaining weight over the long term might appear to be a laudable goal, it is apparently insufficient to favorably affect SBP. ■

The WEAVE Study: Does Special Training in Domestic Violence Improve Outcomes?

Source: Hegarty K, et al. *Lancet* 2013; 382:249-258.

Intimate partner violence (IPV) is a public health problem that knows no boundaries of age, country of residence or origin, economic status, or education. Primary care clinicians, particularly family physicians, are often the first point of clinical contact for victims of IPV, but may lack confidence in their ability to identify and/or address IPV. Hegarty et al report on a trial from Australia in which women who screened positive for concerns about fear of their partner (n = 272) received care from family physicians who were randomized to receive special training in IPV or no intervention. The intervention group physicians participated in the Healthy Relationships Training program, which is intended to provide the ability to respond effectively to women who have experienced IPV and give brief counseling. The primary outcomes of the trial were changes in quality of life (as per the WHO QOL-BREF), safety planning and behavior, and mental health (as per the SF-12) at 1 year.

At 1 year, there was no difference in the primary endpoint between the intervention group and controls. A favorable impact on depression (a secondary endpoint) was seen. However, since the primary endpoint was not achieved, the potential for benefits on depression must remain considered as hypothesis generating. ■

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PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

More Side Effects of Fluoroquinolones Coming to Light

In this issue: New side effects of fluoroquinolones; probiotics and antibiotic-related diarrhea; prostate cancer risk and 5-ARIs; and FDA actions.

New study finds dysglycemia risk

Fluoroquinolones, such as levofloxacin, ciprofloxacin, and moxifloxacin, are useful broad-spectrum antibiotics, but they have been associated with tendinopathy, including tendon rupture and QT interval prolongation. Now, two new potential side effects are coming to light. In a new study from Taiwan, more than 78,000 diabetic patients who received fluoroquinolones were monitored for dysglycemia, including hyperglycemia and hypoglycemia. The study looked at users of levofloxacin, ciprofloxacin and moxifloxacin, cephalosporins, and macrolides. The absolute risk of hyperglycemia was 6.9 per 1000 for moxifloxacin and 1.6 for macrolides. The risk for hypoglycemia was 10.0 for moxifloxacin and 3.7 for macrolides. The adjusted odds ratios for hyperglycemia compared to macrolides were: moxifloxacin 2.48 (95% confidence interval [CI], 1.50-4.12), levofloxacin 1.75 (95% CI, 1.12-2.73), and ciprofloxacin 1.87 (95% CI, 1.20-2.93). For hypoglycemia, the adjusted odds ratios were moxifloxacin 2.13 (95% CI, 1.44-3.14), levofloxacin 1.79 (95% CI, 1.33-2.42), and ciprofloxacin 1.46 (95% CI, 1.07-2.00). The risk of hypoglycemia associated with moxifloxacin was even higher if patients were taking insulin. The authors suggest that fluoroquinolones, especially moxifloxacin, are associated with severe dysglycemia in diabetic patients and that clinicians should "prescribe quinolones cautiously" in diabetic patients (*Clin Infect Dis* published online August 14, 2013. DOI: 10.1093cid/cit439). In related news, the FDA is requiring labeling changes for fluoroquinolones regarding the risk of neuropathy. The FDA Drug Safety Communication states that "serious nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken and may be permanent." The warning is for both oral and parenteral forms of the drugs, but not topicals. The FDA recommends that if a patient develops symptoms of peripheral neuropathy associated with a fluoroquinolone, the drug should be stopped immediately and the patient should be switched to a non-fluoroquinolone antibiotic. Further information can be found at the FDA's website at www.fda.gov/Safety/MedWatch. ■

Probiotics and antibiotic-related diarrhea

Probiotics may not prevent antibiotic-associated diarrhea (AAD), including *Clostridium difficile* infections. That was the finding of a randomized, double-blind, placebo-controlled trial in nearly 3000 inpatients aged ≥ 65 years who were exposed to one or more oral or parenteral antibiotics. Patients were randomized to a multistrain preparation of lactobacilli and bifidobacteria or placebo for 21 days. The rate of AAD was 10.8% in the probiotic group and 10.4% in the placebo group ($P = 0.71$). *C. difficile* was uncommon and occurred in 0.8% of the probiotic group and 1.2% of the placebo group ($P = 0.35$). The authors state that "we identified no evidence that a multistrain

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preparation of lactobacilli and bifidobacteria was effective in the prevention of AAD or CDD." (*Lancet* published online August 8, 2013. doi: 10.1016/S0140-6736(13)61218-0). An accompanying editorial wonders if this study can tip the balance of probiotic evidence, as it was a rigorously performed study vs previous small studies showing a positive effect. But, the current study used only two types of non-pathogenic bacteria (doi: 10.1016/S0140-6736(13)61571-8). Still, the cost effectiveness of routine probiotic use must be questioned based on this study. ■

Prostate cancer risk and 5-ARIs

The debate regarding 5-alpha reductase inhibitors (finasteride [Proscar] and dutasteride [Avodart]) and the risk of prostate cancer continues. Despite good evidence that the drugs reduce the overall risk of prostate cancer, there is also evidence that the drugs may increase the risk of high-grade prostate cancers (Gleason score 7-10). This was a finding of the Prostate Cancer Prevention Trial (PCPT) that was published in 2003. That finding was recently questioned in a study published in the *British Medical Journal* that found no risk of higher-grade prostate cancers (*BMJ* 2013;346:f3406, reported in the August *Pharmacology Watch*). Now, 10 years after the PCPT was originally published as an 8-year study, the 18-year follow-up has been published in the *New England Journal of Medicine*. Of the nearly 19,000 men who underwent randomization in the PCPT, prostate cancer was diagnosed in 10.5% of the finasteride group and 14.9% of the placebo group, a 30% reduction in the rate of prostate cancer (relative risk 0.70; 95% CI, 0.65-0.76; $P < 0.001$). But all of the reduction was in lower-grade prostate cancers. There was a slightly higher rate of high-grade cancer in the finasteride group (3.5% vs 3.0%, $P = 0.05$), but there was no difference in overall mortality. There was also no increase in mortality in men diagnosed with high-grade prostate cancer. The authors conclude that finasteride reduced the risk of prostate cancer by about one-third, and although high-grade cancer was more common in the finasteride group, there was no difference in overall mortality or survival after the diagnosis of prostate cancer (*N Engl J Med* 2013;369:603-610). Dutasteride was also studied in the REDUCE trial and similarly found lower rates of low-grade prostate cancers but increased rates of higher-grade cancers (*N Engl J Med* 2010;362:1192-1202). Some have argued that the higher rate of high-grade cancers is due to higher surveillance and "detection bias," but regardless of the cause, it is reassuring to know that there is no higher risk of mortality, at least in the PCPT. The FDA changed the labeling to both finasteride and dutasteride in 2011 regarding the increased risk of high-grade prostate cancers. ■

FDA actions

The FDA has issued a Drug Safety Communication regarding a case of progressive multifocal leukoencephalopathy (PML) in a patient who was taking fingolimod (Gilenya) for the treatment of multiple sclerosis. This is the first reported case of PML associated with fingolimod in patients who had not previously taken natalizumab (Tysabri). The patient, who lives in Europe, had been on the drug for about 8 months and had previously taken interferon beta-1a, azathioprine, and steroids. Novartis, the manufacturer of fingolimod, indicated it is possible that the patient had PML prior to starting the drug. PML is a rare neurologic disease caused by latent infection with the JC virus. It has been associated with immunosuppressive drugs, including natalizumab.

The FDA has approved a new topical agent to treat facial redness in adults with rosacea. Brimonidine, an alpha-2 agonist, is currently used as an ophthalmic preparation for treating glaucoma. The drug constricts dilated facial blood vessels for up to 12 hours. It is approved in a 0.33% topical gel that is applied once daily. Patients with depression, coronary artery disease, Raynaud's, or other conditions that may be exacerbated by an alpha agonist should use the drug with caution. Brimonidine gel is marketed by Galderma as Mirvaso.

The FDA has approved dolutegravir, a new once-daily HIV integrase inhibitor. It is the third integrase inhibitor on the market after raltegravir and elvitegravir. The drug is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infections in adults and children ≥ 12 years of age weighing at least 40 kg. It may be used in treatment-naïve patients or treatment-experienced patients, including those who have previously taken an integrase inhibitor. Approval was based on four trials in more than 2500 patients that showed efficacy in combination with other antiretrovirals. A fifth trial showed efficacy in HIV-infected children as young as 12 who had not taken an integrase inhibitor. Dolutegravir is marketed by ViiV Healthcare as Tivicay. ■