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PULMONARY & CRITICAL CARE INSIDER

Issue 4

**COMPILED AND REVIEWED BY
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VIEWPOINTS

*VIEWPOINTS COMPILED BY BHARAT BAJANTRI, MD.
ADOPTED FROM PULMCC AND CITED ARTICLES.*

Inside Medicine- Ozempic

We know that the blockbuster drug Ozempic, Wegovy, and other semaglutide-based drugs helps patients lose weight, control their diabetes (thereby lowering rates of serious complications like strokes) and even [prevent heart failure exacerbations](#).

New data show Ozempic helped save lives in patients without diabetes. The new study randomized 16,000 patients ages 45 and older without diabetes but with a history of cardiovascular disease, and a body mass index of 27 or greater (overweight or obesity) to receive either Ozempic injections once per week or placebo (and standard of care) for two years.

The details:

- 16,000 patients, ages 45 and older
- No history of diabetes (laboratory confirmed)
- History of cardiovascular disease (prior heart attack or stroke)
- Body Mass Index of 27 or above (overweight or obesity)
- Blinded randomization. Half received weekly Ozempic injections, half received placebo injections
- Patient outcomes were tracked for 4 years.
- Primary outcome of the study: a composite; death from a heart condition, non-fatal heart attack, or non-fatal stroke

The trial succeeded. Fewer patients in the Ozempic arm had a “primary outcome event.” Think about that. Supposedly this is a diabetes and weight loss drug. Now it’s reducing some deaths, heart attacks, and strokes?

This drug continues to do what so many hyped up drugs failed to do: deliver meaningful results on outcomes that really matter. No drug is harm free—but these ones are truly looking like game-changers for an increasingly population “denominator.”

VIEWPOINTS

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Inhaled Amikacin for VAP ([AMIKINHAL Trial](#))

History of VAP: In 2008, the U.S. government [proposed](#) adding VAP to its “hospital-acquired conditions” list—the ones that it won’t pay for. Hospital administrators put VAP on the kill list. Its incidence was closely tracked, and nonprofit organizations provided [bundles](#) for how to eradicate it. And maybe, noticing all the fuss, some clinicians might have started coding for VAP slightly less often in equivocal cases.

The diagnostic ambiguity is real: the diagnosis of VAP depends on contamination-prone sputum cultures and subjective interpretations of portable chest films in intubated patients (who are usually obese, with some degree of volume overload, often making it hard to say whether a new infiltrate is present). This made VAP hard to track, so CDC invented an odd new epidemiologic entity called “[ventilator-associated events](#)” (which do not require microbiology or chest film interpretation) as a proxy for actual VAPs.

Despite all the increased attention, the U.S. incidence of VAP [remains stubbornly persistent](#): though it declined from 20 cases to 15 per 1000 ventilated patients 2008-2015, the rate then crept back up to 17 per 1000 in 2017. Other estimates are much higher—[10% of critically ill ventilated patients](#), but are also stable over time. (And Medicare never did stop paying hospitals to treat patients for VAP.)

So when a meta-analysis of small trials suggested [nebulized antibiotics could prevent VAP](#), it sparked an aspiration for a large randomized trial.

Investigators randomized 850 patients, ventilated for at least three days in ICUs at multiple centers in France, to receive either nebulized amikacin (20 mg/kg ideal body weight, once a day for three days) or an equivalent amount of nebulized saline, all in opaque canisters prepared off-site.

Patients were tested for tracheal bacterial colonization at the time of randomization; 22% were positive.

VIEWPOINTS

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ADOPTED FROM PULMCC AND CITED ARTICLES.*

Inhaled Amikacin for VAP (AMIKINHAL Trial)

A blinded panel of adjudicators identified positive ventilator-associated pneumonia cases, using a standardized algorithm that included a positive quantitative bacterial culture in a respiratory sample and at least two signs/symptoms of pneumonia (elevated or low white cell count, fever, and/or purulent secretions-plus-abnormal chest film).

After 28 days, the patients receiving amikacin had an absolute 7% fewer cases of ventilator-associated pneumonia (15% vs. 22%). There was no significant increase in adverse events among the amikacin group (and no increase in acute kidney injury). The trial was not powered to test for differences in mortality or length of stay.

Why this does not apply to our patient population ?

Diagnosis of RAP on the basis of positive sputum culture results when treated with nebulized amikacin quit steroids upper airway secretions reducing the rate of VAP diagnosis and not true pneumonia. Ambiguity of diagnosis often leads to either over or under diagnosis. If inhaled amikacin was truly improving VAP then ideally we would see difference in length of mechanical ventilation which was exactly the same in both groups.

Overall the rate of VAP in the study seemed to be quite high with incidence of 22% in the control group. On average incidence of VAP is thought to be close to 10% in which case number needed to treat to prevent one VAP would be 30 which is not cost effective by any means. Lastly indiscriminate use of antibiotics is always feel fully associated with drug resistance.

VIEWPOINTS

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2023 GOLD Guidelines for COPD

Background: The WHO and U.S. National Institutes for Health convened the original GOLD expert panel in 1998 to make recommendations for managing chronic obstructive pulmonary disease (COPD). GOLD now has updated its last comprehensive executive summary, published in 2017 ([NEJM JW Gen Med Jun 15 2017](#) and [Am J Respir Crit Care Med 2017; 195:557](#)).

Key Points

- GOLD proposes a new, more-inclusive definition of COPD that focuses on respiratory symptoms, anatomic area of abnormality (airways and alveoli) and airflow obstruction as demonstrated by forced vital capacity/forced expiratory volume in 1 second (FVC/FEV1) <0.7.
- A new definition of COPD exacerbation also is included; it focuses on dyspnea or cough and sputum that worsen during ≤14 days, with associated inflammation due to airway infection, pollution, or other insult to the airways. [Severity is determined by dyspnea intensity, respiratory rate, heart rate, and oxygen saturation.](#)
- Although cigarette smoking continues to be a predominant cause of COPD, more emphasis is placed on exposure to indoor biomass smoke and air pollution in low- and middle-income countries as a risk factor.
- A new recommendation is made for chest computed tomography if patients have persistent exacerbations, symptoms out of proportion to airflow obstruction, or evidence of air trapping/hyperinflation, to reveal alternate diagnoses or target specific therapies.
- Treatments are determined by (1) degree of airflow obstruction, (2) current symptoms, (3) history of moderate and severe exacerbations, and (4) comorbidities.

VIEWPOINTS

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- Previous treatment categories C and D have been combined into a new category, named E (for exacerbations). GOLD provides new guidance based on blood eosinophil level. [Initial therapy for categories A, B, and E.](#) is as follows:
 - A: Long-acting β -agonist (LABA) or long-acting muscarinic antagonist (LAMA)
 - B: LABA + LAMA (change from monotherapy)
 - E: LABA + LAMA; if blood eosinophils are ≥ 300 cells/ μ L, consider LABA + LAMA + inhaled corticosteroid (ICS). No recommendation is made (at any eosinophil level) for ICS without combined LABA + LAMA.
- For patients with persistent exacerbations despite LABA + LAMA + ICS or for those who have >100 eosinophils/ μ L, roflumilast (for patients with chronic bronchitis and FEV1 $<50\%$ of predicted) or azithromycin (in nonsmokers) can be considered.
- Pulmonary rehabilitation is recommended for patients in treatment groups B and E.
- Recommendations for oxygen therapy, ventilatory support, and lung-volume reduction surgery are unchanged in this update, although endobronchial valve and endoscopic lung-volume reduction surgery now are included.
- Exacerbations should be treated with bronchodilators and prednisone (40 mg daily for 5 days). A 5-to-7-day course of antibiotics is appropriate for patients with increased sputum volume and purulence or for patients on mechanical ventilation.

COMMENT

Six years after the last update, the 2023 GOLD report emphasizes new definitions of both COPD and COPD exacerbation, with the former designed to be more inclusive and the latter to be more functional for clinicians. The most substantial changes to therapy are creating the “E” category, more emphasis on LABA + LAMA combination treatment for most patients, and minimizing use of ICS.

ORIGINAL ARTICLE SUMMARIES:

SAGA OF ANTIBIOTICS IN THE ICU!!! VERSION 2023.

- **A LARGE-SCALE MULTICENTER RETROSPECTIVE STUDY ON NEPHROTOXICITY ASSOCIATED WITH EMPIRIC BROAD-SPECTRUM ANTIBIOTICS IN CRITICALLY ILL PATIENTS, CHEST 2023**
- **ACORN Trial**
- **SMART Trial**

ACORN vs Cefepime – also PulmCCM

[Piperacillin-Tazobactam vs. Cefepime for Kidney Injury and Neurologic Dysfunction \(ACORN Trial\)](#)

Piperacillin-tazobactam, marketed as Zosyn, has been one of the most-prescribed broad spectrum antibiotics for many years, used for its bactericidal activity against most gram-negative and anaerobic bacteria, including Pseudomonas. Cefepime has similar antibacterial activity, and both are widely used in the ICU as empiric coverage in patients with potentially serious gram-negative infections.

Pip-tazo has been repeatedly associated with an [increased risk for acute kidney injury](#) over the past several years, based on retrospective observational studies with risk for confounding. Answering this research question has been made more difficult by pip-tazo's [possible status as a pseudo-nephrotoxin](#) (elevating creatinine levels in the blood without harming the kidneys) and frequent co-administration with vancomycin, a known nephrotoxin. Over the years, dozens of copycat studies (which are relatively easy for academics to churn out) created a steady, low-quality drumbeat of negativity toward Zosyn.

More recently a large multicentric retrospective study (n= 3,089,748) on nephrotoxicity associated with empiric broad-spectrum antibiotics published in CHEST that was also summarized in issue 1 of the newsletter and interpreted as -prescribing empiric antibiotic regimens to critically ill patients, clinicians may consider combination of vancomycin and meropenem or vancomycin and cefepime over vancomycin and Zosyn to reduce risk of nephrotoxicity and adverse clinical events.

ORIGINAL ARTICLE SUMMARIES:

SAGA OF ANTIBIOTICS IN THE ICU!!! VERSION 2023.

The onset of nephrotoxicity with a combination of vancomycin and Zosyn was seen no later than 48-72 hours in the steady. Nevertheless, this was not a randomized controlled trial with many limitations and the ever-debatable pseudo versus true acute kidney injury with Zosyn needed to be accounted for before any definitive conclusions. Thus, stressing the importance of antibiotics stewardship and early de-escalation of antibiotics as this study was designed only to evaluate antibiotic combinations and not individual antibiotics by themselves.

However, secondary analysis of the SMART trial (n=3199) which was a single center (Vanderbilt university 5 ICUs) was concluded that - Among critically ill adults, receipt of piperacillin-tazobactam was not associated with an increased incidence of death, renal replacement therapy (patient centered MAKE30 outcome), or persistent renal dysfunction or a greater number of days alive and free of delirium and coma. However the study certainly has drawbacks (a) Cephalosporins group received both cefepime and ceftrazidime and each have different risk of neurotoxicity, (b) Assessment of neurotoxicity was based on delirium and coma free states which is certainly not an objective measure of neurotoxicity, the true known measures of neurotoxicity like seizures and myoclonus were not measured, © median duration of antibiotics was less than 3 days which may not be adequate antibiotic exposure for toxicity.

For its part, cefepime has been strongly suspected of causing neurologic dysfunction, based on [many case reports](#) and the fact that it crosses the blood-brain barrier in significant concentrations. Cefepime has not been associated with kidney dysfunction. The rumors of Zosyn-induced kidney injury and cefepime-induced neurotoxicity persisted mainly because no one had performed a large randomized trial. Until now.

ORIGINAL ARTICLE SUMMARIES:

SAGA OF ANTIBIOTICS IN THE ICU!!! VERSION 2023.

Investigators randomized 2511 patients in EDs and ICUs at Vanderbilt University, whose attendings intended to prescribe antipseudomonal coverage, to receive either pip-tazo or cefepime (open-label). About three-quarters of patients were also prescribed vancomycin (at similar rates between groups). Patients received antibiotics a median 3 days. At 14 days, there were no differences between groups in the rates of acute kidney injury, need for renal replacement therapy, or death.

Those receiving cefepime were adjudicated to have greater rates of neurologic dysfunction (a positive CAM-ICU test or RASS score -4 or -5). At 14 days, patients receiving cefepime had 11.9 days free of delirium and coma vs. 12.2 days for those prescribed pip-tazo. (Higher = better for days free of bad things.) Having said that delirium assessments in different centers had variable practices creating some potential for unmeasured bias.

The absolute rates of neurologic dysfunction (as defined above) were 3.4% higher in the cefepime group (20.8% vs 17.3%). If broadly true, that would signify a number needed to harm of about 33 to induce delirium or coma with cefepime, relative to Zosyn.

Cefepime crosses the blood-brain barrier, and dozens of case reports have associated the drug with seizures, encephalopathy, delirium, and coma, with a [possibly increased incidence of neurologic adverse effects among patients with renal failure or sepsis.](#)

Zosyn seems to have been cleared of all renal wrongdoing and to have won this round against cefepime. It will be interesting to see if and how cefepime's potential neurotoxicity is further tested.

ORIGINAL ARTICLE SUMMARIES:

ALBUTEROL-BUDESONIDE PRESSURIZED METERED DOSE INHALER IN PATIENTS WITH MILD-TO-MODERATE ASTHMA RESULTS OF THE DENALI DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL- CHEST

Aim of Study:

The MANDALA trial encouraged the work for the DENALI trial, which was conducted to address the US FDA combination rule; the requirement to demonstrate efficacy of each component in a combination medicinal product. The DENALI trial evaluates whether both albuterol and budesonide contribute to the efficacy of the albuterol-budesonide combination pressurized metered-dose inhaler in patients with asthma?

Methods, Inclusion, Exclusion-

This 12-week phase 3 double-blind trial randomized 1,001 patients (10 children aged 4-11 years and 990 patients aged 12 years and up) with mild-to-moderate asthma 1:1:1:1:1 to four-times-daily.

Trial medication randomization is as follows.

- 197 Albuterol-budesonide combination 180/160 µg
- 204 Albuterol-budesonide combination 180/80 µg
- 201 Albuterol 180 µg alone
- 200 Budesonide 160 µg alone
- 199 Placebo

The dual-primary efficacy end points determined the therapeutic contribution of each mono-component to lung function efficacy; these were

1. Change from baseline in Forced expiratory volume (FEV₁) area under the curve from 0 to 6 hours; averaged over the 12-week randomized treatment period to assess the contribution of albuterol
2. Change from baseline in trough FEV₁ at week 12 to assess the contribution of budesonide.

In-clinic visits were in weeks 1, 4, 8, and 12. All patients were provided an eDiary to record peak expiratory flow measurements, trial medication use, and asthma symptoms. Efficacy and safety/adverse events analysis were included.

ORIGINAL ARTICLE SUMMARIES:

ALBUTEROL-BUDESONIDE PRESSURIZED METERED DOSE INHALER IN PATIENTS WITH MILD-TO-MODERATE ASTHMA RESULTS OF THE DENALI DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL- CHEST

Results:

- 928 patients (92.7%) completed the trial.
- Patients recorded administering a median of 93.8% of their trial medication.
- Compliance was similar across treatment groups.
- Adverse events occurred in 31% to 35% of patients across the treatment groups.
- Most common adverse events were nasopharyngitis and headache. There were no deaths in the trial.

It was determined by the end of the 12-week trial that albuterol and budesonide both contributed to the lung function efficacy of the albuterol-budesonide combination, as assessed by change from baseline in FEV₁ area under the curve from 0 to 6 hours and in trough FEV₁.

TABLE 2 | Dual-Primary Efficacy End Points: Efficacy Population, ≥ 12 Years

Primary Efficacy End Point	Step in Testing Sequence	Comparisons	LSM	Comparison Between Groups	
				Difference in LSM (95% CI)	P Value (Two-Sided)
FEV ₁ AUC _{0-6h} , change from baseline over 12 wk, mL ^a	1	Albuterol 180 µg (n = 195) vs placebo (n = 196)	157.2 vs 96.7	60.5 (7.7-113.4)	.025
	2	Albuterol-budesonide 180/160 µg (n = 197) vs placebo (n = 196)	258.6 vs 96.7	161.9 (109.4-214.5)	< .001
	3	Albuterol-budesonide 180/160 µg (n = 197) vs budesonide 160 µg (n = 199)	258.6 vs 178.0	80.7 (28.4-132.9)	.003
Trough FEV ₁ , change from baseline at week 12, mL	4	Budesonide 160 µg (n = 187) vs placebo (n = 175)	108.9 vs 35.6	73.3 (4.4-142.2)	.037
	5	Albuterol-budesonide 180/160 µg (n = 186) vs placebo (n = 175)	135.5 vs 35.6	99.9 (30.9-168.8)	.005
	6	Albuterol-budesonide 180/160 µg (n = 186) vs albuterol 180 µg (n = 172)	135.5 vs 2.7	132.8 (63.6-201.9)	< .001
	7	Albuterol-budesonide 180/80 µg (n = 184) vs placebo (n = 175)	123.5 vs 35.6	87.9 (18.8-156.9)	.013
	8	Albuterol-budesonide 180/80 µg (n = 184) vs albuterol 180 µg (n = 172)	123.5 vs 2.7	120.8 (51.5-190.1)	< .001

AUC_{0-6h} = area under the curve from 0 to 6 h postdose; LSM = least-squares mean.

^aThe LSM was calculated as the difference between treatment groups average over all time points during the randomized treatment period.

Clinical Interpretation:

The DENALI trial confirms that both components of the albuterol-budesonide combination contribute to lung function efficacy.

ORIGINAL ARTICLE SUMMARIES:

ALBUTEROL-BUDESONIDE PRESSURIZED METERED DOSE INHALER IN PATIENTS WITH MILD-TO-MODERATE ASTHMA RESULTS OF THE DENALI DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL- CHEST

ICS/LABA (Formoterol) Reliever – mild asthma

- Reduced severe exacerbation by 55% compared to SABA
- Similar risk of severe exacerbation compared to ICS maintenance + SABA prn
- Decreased asthma related hospitalization/ED/urgent care clinic by 32% compared to ICS maintenance + SABA prn

ICS/LABA (Formoterol) Reliever – moderate to severe asthma

- ICS/LABA reliever + ICS/LABA maintenance better than SABA + ICS/LABA maintenance by reduction severe exacerbation from 20-32% (depending on dose and type of ICS and LABA)

Although this ICS/formoterol reliever therapy approach is preferred, maintenance ICS or ICS/ LABA therapy together with SABA reliever use may be recommended in some situations, such as for patients on such a regimen whose asthma is well controlled and who are not at high risk of exacerbations, in those with poor ICS/formoterol inhaler device technique despite training, and in populations in which ICS/formoterol products are not available or affordable

ICS/SABA - mild asthma

- Beclomethasone + Albuterol reduced any exacerbation by 54%

ICS/SABA - moderate to severe asthma

- Budesonide + SABA compared to SABA alone reliever decreased severe exacerbation by 17-27% (based on ICS used)

ORIGINAL ARTICLE SUMMARIES:

ALBUTEROL-BUDESONIDE PRESSURIZED METERED DOSE INHALER IN PATIENTS WITH MILD-TO-MODERATE ASTHMA RESULTS OF THE DENALI DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL- CHEST

ICS/albuterol reliever therapy can be used with all other maintenance ICS/LABA products regardless of the specific LABA. In contrast, ICS/formoterol reliever therapy is restricted to ICS/formoterol maintenance treatment in moderate and severe asthma. Disadvantages include the requirement to use at least two separate inhalers in moderate and severe asthma, and the lesser efficacy with ICS/albuterol vs ICS/formoterol reliever therapy because of the greater efficacy of formoterol vs SABA in reducing severe exacerbation risk. An alternative to combination ICS/albuterol reliever treatment is the use of separate ICS and SABA inhalers at the same time as reliever therapy. There is an evidence base for this approach's efficacy and safety in both children and adults; however, there is a major practical limitation in using two separate inhalers at the same time, rather than a single combination reliever inhaler.

Barriers to implementation of LABA/ICS as a reliever inhaler include reluctance among providers and patients secondary lack of experience. Most importantly, pharmaceutical industry's promotion of alternative options, requirement for regulatory approval, availability, and cost (even though budesonide/ formoterol is on the World Health Organization essential medicines list). The situation in the United States has been a particular focus of concern, because despite ICS/formoterol maintenance and reliever therapy being recommended by the Global Initiative for Asthma and National Asthma Education and Prevention Program guidelines, and the regulatory approval of budesonide/formoterol in more than 120 countries, no ICS/formoterol products are currently approved by the US Food and Drug Administration for reliever use, although budesonide/albuterol has recently been approved by the US Food and Drug Administration for use as a reliever across the range of asthma severity.

ORIGINAL ARTICLE SUMMARIES:

ALBUTEROL–BUDESONIDE FIXED-DOSE COMBINATION RESCUE INHALER FOR ASTHMA, NEJM

Aim of Study:

This publication describes the MANDALA trial. The aim of this study was to evaluate the safety and efficacy of the albuterol–budesonide, a newer combination rescue medication, compared with the as-needed use of albuterol alone, for patients with symptomatic asthma.

Methods & Inclusion

The MANDALA trial was a multinational, phase 3, double-blind, randomized, parallel-group, event driven study. 5620 patients were enrolled in trial period, 12/27/18 to 7/30/21.

- 3132 were randomized.
- 3123 were assessed with focus on efficacy.
- 3127 were assessed with focus on safety.

Inclusion Criteria:

- Aged 4 and older
- Symptomatic asthma
- One or more defined severe asthma exacerbations in the previous 12 months
- A forced expiratory volume in 1 second (FEV₁) of 40 to less than 90% of the predicted normal value
- In clinic visit measure of FEV₁ reversibility of at least 12%
- A score on the Asthma Control Questionnaire–5 (ACQ-5) of 1.5 or greater (indicates poorly controlled asthma).

Adults and adolescents were randomly assigned in a 1:1:1 ratio to one of three treatment groups:

- the higher-fixed- dose combination group: albuterol 180 µg + budesonide 160 µg
- the lower-fixed-dose combination group: albuterol 180 µg + budesonide 80 µg
- the albuterol-alone group: albuterol 180 µg

Each dose consisting of two actuations (equal halves) and delivered through a pressurized metered-dose inhaler. The maximum daily dose of a trial medication was 12 inhalations (i.e., 6 doses) for all the patients.

Children (defined aged 4-11) were not randomized in the higher dose combination group, due to concerns.

ORIGINAL ARTICLE SUMMARIES:

ALBUTEROL-BUDESONIDE FIXED-DOSE COMBINATION RESCUE INHALER FOR ASTHMA, NEJM

All patients were educated on the proper technique for inhaler and their technique was evaluated by staff at trial site. Rescue use was limited to the trial medications during study and additional fast-acting bronchodilators were prohibited. Unless clinically indicated, changes in maintenance therapy were discouraged.

Results:

At trial end, the primary efficacy measurement was the first event of severe asthma exacerbation in a time-to-event analysis. Total systemic glucocorticoid exposure per patient was calculated and analyzed. Evaluation/Validated questionnaires used for patients, with consideration to age like; ACQ-5, the AQLQ+12, and the PAQLQ at week 24.

Patients 4 to 6 years of age completed the PAQLQ with the help of a caregiver.

At baseline patients were given the ACQ-5: Mean score was 2.6 across the three trial groups, a result indicating poorly controlled asthma. At end point, (week 24), a response (an improved score of at least 0.5 points) was observed each group:

A response on the ACQ-5

- 66.8% higher-dose combination group
- 64.7% lower-dose combination group
- 62.1% in albuteral alone group

A response on the AQLQ+12

- 51.1% in higher-dose combination group
- 49.5% in lower-dose combination group
- 46.4% in albuterol alone group

The risk of severe asthma exacerbation was significantly lower, by 26%, in the higher-dose combination group than in the albuterol-alone group.

ORIGINAL ARTICLE SUMMARIES:

ALBUTEROL-BUDESONIDE FIXED-DOSE COMBINATION RESCUE INHALER FOR ASTHMA, NEJM

Safety End Points: The incidence of adverse events was similar in the three trial groups; most common were nasopharyngitis, headache, and upper respiratory tract infection. Occurrence of adverse events was 46.2% in the higher-dose combination group, 47.1% in the lower-dose combination group, and 46.4% in the albuterol-alone group. No deaths were considered by the trial investigators to be related to the trial medication.

Strength: Low dropout rate, with 93% of the patients completing at least 24 weeks of the treatment period. Particularly of note since trial was conducted globally during Covid-19 pandemic.

Clinical Interpretation:

Due to low risks and the greater efficacy (both aspects of patient centric as well as severe asthma exacerbation) of the fixed-dose combination than of albuterol alone, could replace short-acting β_2 -agonists as rescue therapy in patients with moderate-to-severe asthma.

ORIGINAL SUMMARIES:

ANOTHER RESCUE THERAPY OPTION FOR PATIENTS WITH MODERATE-TO-SEVERE ASTHMA- EDITORIAL

The MANDALA trial was able to show the fixed dose rescue medication combo of albuterol-budesonide reduced the risk of severe asthma exacerbations by 26% as compared with albuterol alone. Results of the SMART trial showing use of single maintenance and reliever inhaler therapy

The 2020 guidance update from the National Asthma Education and Prevention Program (NAEPP) and , driven by the results of the SMART trial, the use of single maintenance and reliever inhaler therapy (ICS/ formoterol) for moderate-to-severe asthma, as well as the European Respiratory Society short guidelines for the use of as-needed ICS/formoterol in mild asthma recommending use of ICS/formoterol over regular ICS alone with SABA as needed or only SABA as needed for mild asthma brings up concerns for its effectiveness as compared with combined albuterol–glucocorticoid rescue-inhaler therapy added to standard asthma-control regimens from the MANDALA trial.

The aim of the SMART trial was the comparison between formoterol and albuterol as a component of the inhaled glucocorticoid-containing rescue therapy. That study observed a 32% reduction in the risk of exacerbations for 8483 patients.

Head-to-head studies of the same inhaled glucocorticoid combined with either formoterol or albuterol as rescue therapy should be done to determine superior treatment.

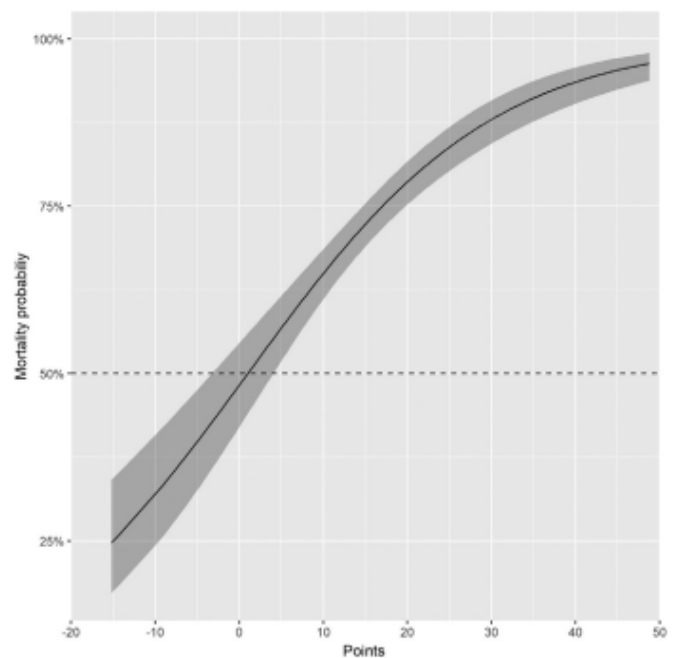
SNAPSHOTS

RESCUE IHCA – Not perfect but maybe the best we have !!!

The externally validated RESCUE-IHCA score enables a clinician to estimate at the bedside in real time, with 72% accuracy, a probability of death ranging from 22% to >99% using [patient characteristics](#) known at the time of cardiac arrest, without waiting for laboratory values. Moreover, we found that 5 of the variables associated with survival were related to the conditions of the arrest or to the patient (age, patient type, history of renal insufficiency, time of day, and initial rhythm), whereas only 1 was a potentially modifiable intra-arrest feature (duration of arrest). (AUC 0.70)

Age	
≤20 y	2
Each additional 10 y	+2
Preexisting renal insufficiency	
Yes	+8
Time of day	
3 PM to 10:59 PM	+4
11 PM to 6:59 AM	+13
Illness category	
Medical cardiac	-2
Surgical cardiac	-11
Surgical noncardiac	-6
Presenting rhythm	
PEA	-1
pVT	-5
VF	-8
Palpable pulse initially	-5
Duration of cardiac arrest	
Each 10 min	+2

FIGURE 3 Predicted Probability of Death Across Points



Curve with 95% CI shading showing the association between score points and mortality of in-hospital death among the derivation cohort.

SNAPSHOTS

TRY NOT TO MESS HUMAN PHYSIOLOGY? MAYBE

Acetazolamide for metabolic alkalosis complicating respiratory failure with chronic obstructive pulmonary disease or obesity hypoventilation syndrome: a systematic review

Four studies with 504 patients were included. 99% of patients included had chronic obstructive pulmonary disease. No trials recruited patients with obstructive sleep apnea. 50% of trials recruited patients requiring mechanical ventilation. The risk of bias was low overall.

WHAT IS ALREADY KNOWN ON THIS TOPIC: Acute respiratory failure in patients with chronic hypercapnic respiratory disease may be associated with metabolic alkalosis. Acetazolamide can reduce serum pH and may reduce ventilatory suppression in this patient population although benefits on mortality or ventilation duration have not been identified.

WHAT THIS STUDY ADDS: Acetazolamide has no statistically significant effects on mortality, duration of ventilation or duration of hospitalization in patients with acute respiratory failure and metabolic alkalosis in the context of chronic obstructive pulmonary disease or obesity hypoventilation syndrome.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY: Larger well-powered clinical trials are required to confirm whether the use of acetazolamide has any significant benefits or harm for patients with acute respiratory failure and metabolic alkalosis in the context of chronic hypercapnic respiratory disease

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