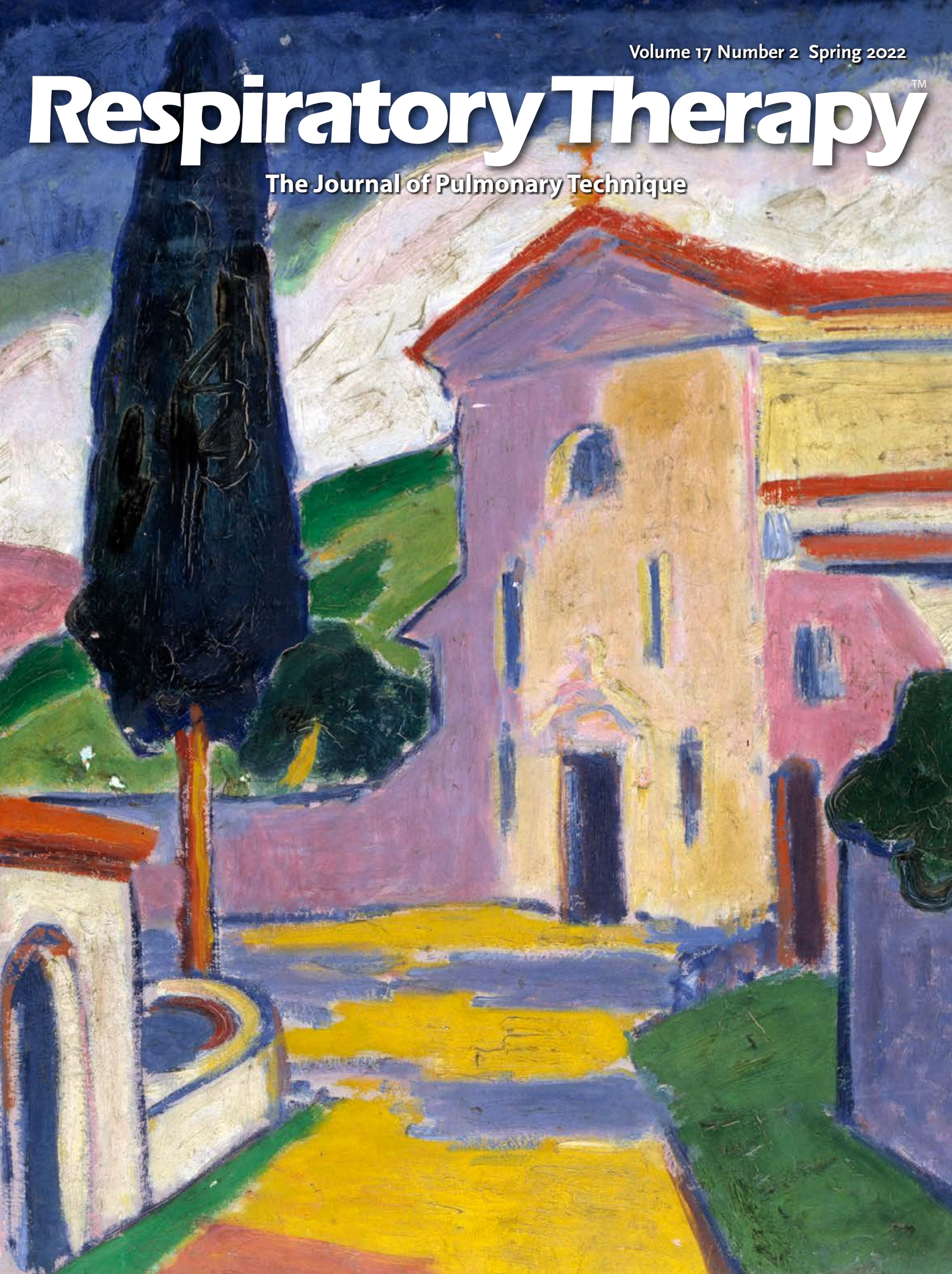
Volume 17 Number 2 Spring 2022

Respiratory Therapy™

The Journal of Pulmonary Technique



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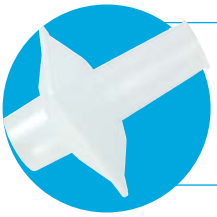

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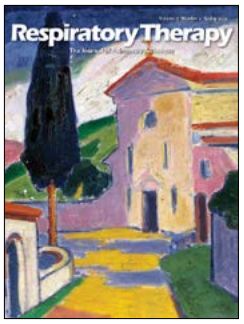

Respiratory Therapy™
The Journal of Pulmonary Technique
Vol. 17 No. 2
Spring 2022

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News

■ Spring 2022

Correction on Vitalograph Spotlight

The spotlight from Respiratory Therapy Winter edition should read as: The Vitalograph new Pneumotrac spirometer equipped with new Spirotrac®6 is the most advanced, accurate, and durable spirometer available. Not only is testing simple with a click of the space bar, but the software is nimble enough for customizations of workflow, reports, EMR interfacing, and beyond. In addition, the 2019 ATS grading standard is incorporated in Spirotrac®6 and our Bacterial/Viral Filter keep your patients safe from cross contamination from many viruses including the Flu and Covid-19.

We apoligize for the misprint.

FDA Okays New Monoclonal Antibody That's Effective Against Omicron

The FDA issued an emergency use authorization (EUA) for bebtelovimab, a monoclonal antibody that "retains activity against Omicron," the agency said. Bebtelovimab is authorized for the treatment of mild to moderate COVID-19 in individuals ages 12 and up who are at risk of progressing to severe disease. Importantly, "laboratory testing showed that bebtelovimab retains activity against both the Omicron variant and the BA.2 Omicron subvariant," the agency added, without providing any more specifics. The antibody is not authorized for hospitalized patients or those requiring oxygen therapy, as it has not been studied in this population and could worsen clinical outcomes, FDA said. "Today's action makes available another monoclonal antibody that shows activity against Omicron, at a time when we are seeking to further increase supply," said Patrizia Cavazzoni, MD, director of the FDA's Center for Drug Evaluation and Research, in a statement. Data supporting this EUA came from the phase II BLAZE-4 trial, which in part enrolled 150 high-risk patients who were randomized to receive either bebtelovimab alone or in combination with other monoclonal antibodies. An additional 176 patients received the drug with other monoclonal antibodies in an open-label arm of the trial. FDA said that COVID-related hospitalizations and deaths were lower among patients who received bebtelovimab alone or in combination with other antibodies versus those who received placebo, but "conclusions are limited as these data are from different trials that were conducted when different viral variants were circulating and baseline risk factors varied."

Infant Bronchiolitis Subtype May Predict Asthma Risk

Bronchiolitis is the leading cause of infant hospitalizations in the United States and Europe, and almost one third of these patients go on to develop asthma later in childhood. But a multinational team of researchers has presented evidence that could avoid that outcome. They identified four different subtypes of bronchiolitis along with a decision tree that can determine which infants are most likely to develop asthma as they get older. Reporting in the journal eClinical Medicine, Michimasa Fujiogi, MD, of Massachusetts General Hospital and Harvard University, Boston, and colleagues analyzed three multicenter prospective cohort studies that included a combined 3081 infants hospitalized with severe bronchiolitis. "This study added a base for the early identification of high-risk patients during early infancy," Fujiogi said in an interview. "Using the prediction rule of this study, it is possible to identify groups at high risk of asthma during a critical period of airway development — early infancy." The researchers identified four clinically distinct and reproducible profiles of infants hospitalized for bronchiolitis:

- A: characterized by a history of breathing problems and eczema, rhinovirus infection, and low prevalence of respiratory syncytial virus (RSV) infection.
- B: characterized by the classic symptoms of wheezing and cough at presentation, a low prevalence of previous breathing problems and rhinovirus infection, and a high likelihood of RSV infection.
- C: the most severe group, characterized by inadequate oral intake, severe retraction at presentation, and longer hospital stays.

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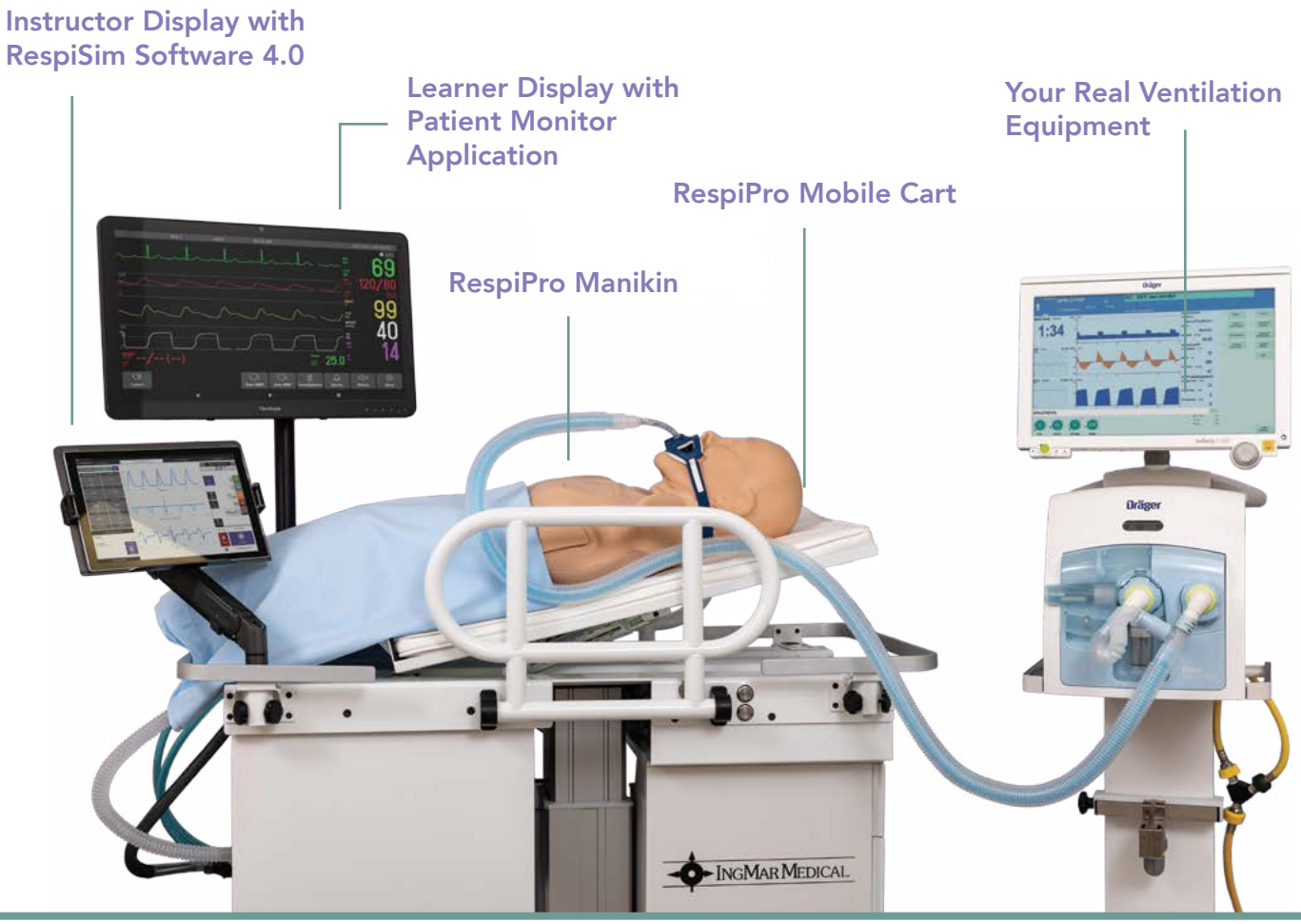

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- D: the least ill group, with little history of breathing problems, but inadequate oral intake with no or mild retraction.

Infants with profile A had the highest risk for developing asthma — more than 250% greater than with typical bronchiolitis. They were also older and were more likely to have parents who had asthma — and none had solo-RSV infection. In the overall analysis, the risk for developing asthma by age 6 or 7 was 23%.

FDA Delays Action on Pfizer Vaccine for Kids Under 5

The FDA said it would delay a decision on authorizing the use of the Pfizer vaccine for younger children until data on the effects of three doses is available. Peter Marks, MD, director of the FDA's Center for Biologics Evaluation and Research, said the plan for a meeting next week of the FDA's Vaccines and Related Biological Products Advisory Committee was to "understand if two doses would provide sufficient protection to move forward." Pfizer has asked the FDA to authorize the use of its mRNA vaccine for children under the age of 5. But, Marks said, "in looking through the data we realized now … that at this time it makes sense for us to wait until we have the data of the evaluation of a third dose before taking action." In response to a question, Marks said the decision should be reassuring for parents and the public. "If we feel something doesn't meet (our) standard, we can't go forward," he said. "Rather than an issue of having anyone question the process, I hope this reassures people that the process has a standard." Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, predicted in January that the Pfizer vaccine for younger kids could be available this month. But, he also predicted three doses would be required. Pfizer announced previously that it planned to submit data to the FDA during the first half of 2022 if the three-dose study was successful. At that time, Pfizer said it didn't identify any safety concerns with the 3-microgram dose for children ages 6 months to 4 years, which is much lower than the 30-microgram dose given to adults.

Identifying Severe Pulmonary Hypertension in Patients With COPD

Patients with severe pulmonary hypertension (PH) and chronic obstructive pulmonary disease (COPD) can now be identified using three widely available clinical variables, all of which can be measured non-invasively, a single-center, retrospective analysis indicates. "All PH is prognostically relevant in COPD, but severe PH is associated with severely decreased survival, and it is frequently associated with a different phenotype of COPD, with less severe airway obstruction but more severe diffusion [capacity] and more severe hypoxemia as well," Gabor Kovacs, MD, associate professor of pulmonology, Medical University of Graz, Graz, Austria, explained. "We believe that patients with this specific phenotype might benefit from individualized therapy, but we need to identify them first and we need non-invasive tools to [select out] patients with this phenotype from the large number of COPD patients without it," he added. The study was published online in the journal CHEST. A total of 142 patients with COPD who had undergone clinically indicated right heart catheterization for suspected PH were included in the analysis. "The diagnosis of COPD and the severity of airflow limitation were established according to the GOLD [Global Initiative for Chronic Obstructive Lung Disease] recommendations," Kovacs and colleagues note

Stratified for severity of PH, 74 participants had severe PH, 45 had moderate PH, and only 23 patients had no PH, investigators observed. COPD with severe PH was defined as a mean pulmonary arterial pressure (mPAP) ≥ 35 mm Hg or mPAP ≥ 25 mm Hg with a low cardiac index of less than 2.0 L/min/m2.

Continued on page 16…

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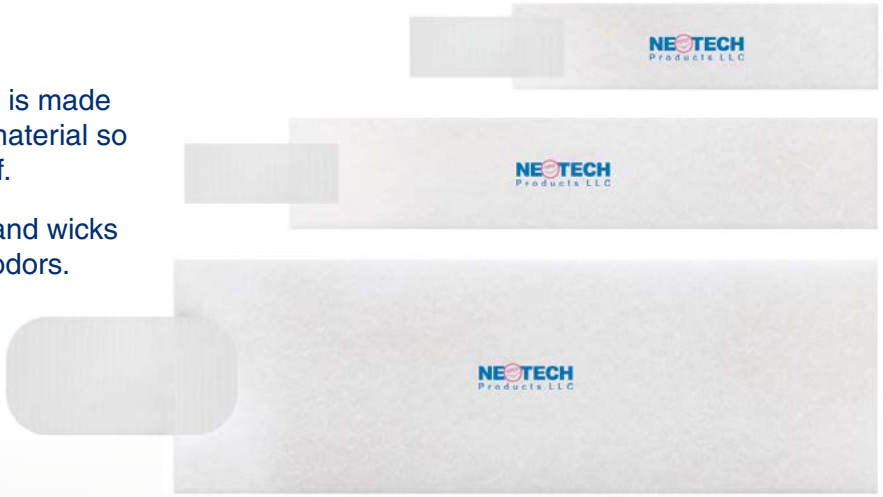

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PRODUCT PROFILE

Siemens Healthineers

epoc Blood Analysis System: now with the new NXS Host

Enhancing performance, workflow efficiency, and data security

The epoc Blood Analysis System (Siemens Healthineers USA, Tarrytown, NY) is a point-of-care (POC), patient-side testing solution that delivers a full menu of laboratory-accurate tests, including blood gases, a basic metabolic panel, hematocrit, and lactate, in less than 1 minute after sample insertion, making it ideal for acute patient populations. The epoc system consists of three components: the epoc blood gas, electrolyte, and metabolite (BGEM) Test Card; the epoc Reader; and the NXS Host Mobile Computer.

epoc Blood Analysis System

epoc Test Card

epoc Test Card[1]

This system was initially launched in 2006 with a Blood Gas and Electrolyte (BGE) panel that included blood gases (pH, pCO_2, pO_2), electrolytes (Na+, K+, Ca++), and hematocrit (Hct). Over time, this test panel was expanded, with glucose added in 2009, lactate in 2010, creatinine (Crea) and chloride (Cl-) in 2012, and blood, urea, nitrogen (BUN) and total carbon dioxide (TCO_2) in 2018.

The current Test Card, the BGEM card, consists of 13 analytes, including blood gases (pH, pCO_2, pO_2), a basic metabolic panel (Na+, K+, Ca++, Cl, glucose, creatinine, BUN, TCO_2), and hematocrit and lactate. With this full panel of analytes, the clinical utility of the epoc system spans all settings in the hospital system.

BGEM Test Cards are single-use and stored at room temperature until expiration, which reduces the time, space, and equipment involved in managing inventory that requires refrigeration.[2] The Test Card contains an internal barcode to identify the card type, expiration date, and serial and lot numbers. With a single Test Card, inventory management, quality control/management, and patient testing are simplified throughout the hospital. The Test Card contains a port for introducing the blood sample, an array of sensors on a sensor module, and a calibration fluid reservoir. The Test Card generates electrical signals proportional to analyte concentrations in the sample.

epoc Reader[1]

The epoc Reader is a battery-powered, portable device that contains an internal barcode scanner and a Test Card slot. It reads the epoc Test Card during a blood test, informs the operator of test progress via status indicators, and measures electrical signals from the Test Card sensors. The Reader transmits test results wirelessly via BLUETOOTH to the epoc Host.

epoc Host[1]

The epoc Host is a dedicated-use, mobile computer with epoc Host software installed. It communicates wirelessly via BLUETOOTH with the epoc Reader, calculates analytical data from sensor data sent by the epoc Reader, and displays results.

epoc Test Process[1]

To initiate a test, you insert an epoc Test Card into the Reader. The Reader reads the barcoded information on the card (If the card is expired, an error message appears). The Reader then performs an internal calibration process to ensure Test Card quality. This calibration prior to sample introduction helps to minimize the need for sample redraws. When card calibration is complete, you introduce the sample through the port on the Test Card.

Only 92 µL of blood is required for the full panel of tests from an arterial, venous, or capillary whole-blood sample. This small sample size helps conserve blood, which is important in critically ill patients for whom repeated blood draws can lead to anemia.[3] After you add the sample, the system analyzes it and provides immediate results at the patient's side. This eliminates the need to transport samples to the laboratory, minimizing sample-quality degradation prior to testing, and helps ensure that test results reflect the patient's immediate condition.

The epoc Blood Analysis System provides electronic patient documentation, critical result management, and positive patient identification, which reduces the opportunity for misidentification of patients and/or medical errors.

When the test is complete, the epoc NXS Host displays the results and wirelessly and securely transmits them to the institution's LIS/HIS/EMR. This allows healthcare personnel to receive, review, document, and respond to results immediately while remaining at the patient's bedside.

The latest innovation: epoc Blood Analysis System with new NXS Host[1,2]

In July 2021, Siemens Healthineers introduced the epoc Blood Analysis System with NXS Host to the US market. The epoc system continues to provide all the utility of the original analyzer—accurate, critical test results at the point of care in less than a minute—with additional benefits enabled by a new, intuitive software application that further advances point-of-care testing.

The new NXS Host was developed incorporating caregiver suggestions that enhance performance and streamline testing workflow. The new Host is powered by ANDROID, providing advanced processing power and expanded memory for fast response

epoc NXS Host

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time. It includes a 5-inch screen with HD resolution and vibrant display, glove-ready touchscreen, and on-screen keyboard display.

The NXS Host user interface is intuitive and workflow-driven, complete with audio and visual guidance that directs the operator through the test procedure. Additionally, test results are color-coded to provide easy identification of normal, out of reference range, and critical values. These color-coded test results are promptly and securely reported and transmitted in real time to the institution's LIS/HIS/EMR. This enables caregivers to quickly initiate action in response to critical results, without having to leave the patient's side.

"Effective point-of-care testing requires instruments that deliver quick results, are easy to use, and offer safeguards both for patient security and quality test results," according to Christoph Pedain, PhD, Head of Point of Care Diagnostics, Siemens Healthineers. "The epoc System with the new NXS Host offers clinical workflow improvements so that frontline healthcare workers can get comprehensive critical care test results quickly and accelerate care for their patients."[4]

Please visit siemens-healthineers.us/epocnxs for more information on how the epoc Blood Analysis System can meet your testing needs.

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3 Page C, et al. Blood conservation devices in critical care: a narrative review. Ann Intensive Care. 2013; 3:14. doi: 10.1186/2110-5820-3-14

4 https://www.siemens-healthineers.com/en-us/press-room/press-releases/fdaclearanceepocnxshostmobilecomputer.html. Accessed 1-17-22.

Retraction: Using Simulation-based Mastery Learning to Teach Residents to Manage Mechanical Ventilators

We are retracting an article that was published in our Winter 2022 issue: "Using Simulation-based Mastery Learning to Teach Residents to Manage Mechanical Ventilators," written by Chris Campbell (the article has been removed from the online issue).

We removed the article after the American Thoracic Society, publisher of the journal *ATS Scholar* (https://www.atsjournals.org/journal/ats-scholar), informed us that extensive sections of the article had been reprinted without permission from the *ATS Scholar* article "Impact of Simulation-based Mastery Learning on Resident Skill Managing Mechanical Ventilators" by Clara J. Schroedl, Alexandra Frogameni, Jeffrey H. Barsuk, Elaine R. Cohen, Lakshmi Sivarajan, and Diane B. Wayne (ATS Scholar 2020;2[1]:34-48, https://dx.doi.org/10.34197/ats-scholar.2020-0023OC).

The *ATS Scholar* article was published under a Creative Commons Attribution Non-Commercial No Derivatives License 4.0, an open access license that does not permit commercial reuse of content without permission. In addition, although a previous conference abstract version of the article (https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A6299) was included in the reference section, the reference to the *ATS Scholar* article had been omitted.

Respiratory Therapy apologizes to the authors of the *ATS Scholar* article and to the journal.

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Listen, Learn, and Then Lead

An Interview with Robert L Joyner, Jr, PhD, RRT, RRT-ACCS, FAARC, Special Assistant to the Provost for Healthcare Programming Associate Dean at Richard A Henson School of Science & Technology, and Director to the Respiratory Therapy Program, Salisbury University

Tell us about your early days as a respiratory therapist. What brought you to the field?


Robert L Joyner

Robert L Joyner: From an early age, I knew that I wanted to work in medicine and specifically work with patients. I went to college with the intent to go to medical school. In my second year, I needed to provide additional support for schooling and began looking for jobs in hospitals nearby. It didn't matter what the job was, just that it was in a hospital. I came across an ad for a certified respiratory therapy technician (CRTT – it was 1987), and called for an interview. I didn't know what a CRTT was, but things like that had never stopped me before. A motto that I still have today is that the worst that can happen is that they can say no. And licensure did not exist in Maryland at that point.

I met with the manager, and his words to me were, "Well, you've taken an A&P class and did pretty well. You are really young (I was 20). Let's give it a shot and see how this works out." I started a few days later, attending my first code within minutes of clocking in. I was mortified and troubled for about a week. I had a talk with my mom about my experience and she told me that I had never let difficulty stop me before and asked if I liked what I was doing. She had me verbalize that yes, I did, and I was hooked. Shortly after that, I was asked by a physician to set up an external IMV bag with a Hudson H-valve to a patient who was receiving ventilation from a Puritan Bennett MA-1. The patient was obviously air-hungry. I had to tell the physician that I didn't know how. He said, "Then—I don't need you here." My honest statement let me to understand that I was no help to the patient or the physician. I was just a spectator to the events that were occurring, and I did not like that feeling. I wanted to help.

I swore to myself that I would never again be in a position where I couldn't do the best for the patient. I learned of California College for Health Sciences and started the program immediately. I began the program in January of 1988, completed the program in April of 1988, and was enrolled at Salisbury University to get a baccalaureate degree in respiratory care by September 1988. I graduated in 1991 with a BS in respiratory care. I travelled with my wife (Lisa) who is also a respiratory therapist to Tulane University Medical Center in New Orleans, LA for a single assignment. I very quickly recognized that I wanted and needed to go back to school. I did not know enough to be involved with some of the patient care I was doing (e.g., pressure control-inverse ratio ventilation, neonatal and pediatric heart defects, etc.). I applied and was turned down from Dartmouth in 1991. We moved to New Hampshire to work at Dartmouth-Hitchcock Medical Center and the following year I applied again. I was accepted into the Department of Physiology at Dartmouth Medical School and studied pulmonary hypertension. Mostly I learned how much I don't know. I graduated with a PhD in physiology in 1998.

If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net

Who were your mentors? What did they contribute to your career?

RLJ: Wes White, the manager who hired me first taught me that you need to give people a chance. He is a wonderful person and I will forever be indebted for the opportunities that he provided me.

Hal Manning, MD – A mentor from Dartmouth who taught me to critically think and ask thoughtful questions. He is forever in my thoughts when I read papers or listen to a discussion.

Jay Leiter, MD – My thesis mentor. Likely the smartest, most thoughtful person I have ever met. He plays more of a parental roll for me than he will ever know. He taught me not only how to learn, but how to be kind to others who are going through their own struggles.

Given this opportunity to write about my experiences I would like to thank them for everything they have done for me. I would not be who I am without their guidance.

What prompted you to move into a leadership/education position?

RLJ: I got into patient care because I wanted to help patients. 20 years into my professional practice I became concerned with the knowledge of some leaders and began to realize that I needed to participate in their education. Being in higher education allows an individual's influence to be exponential and that is what I am currently hoping that is happening.

How did furthering your education contribute to your career path?

RLJ: Honestly, I would like to state this question a different way. My education did not cause my career path. It opened doors that

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I wanted to open and has facilitated my involvement in decision making that I would not have otherwise been able to do. Without my education, I would be left to criticizing others without the opportunity to participate in the decisions that are being made. I have a healthy respect for difficult decisions and I am much less likely these days to complain without also forwarding a solution. Decisions are the result of problems and constraints on solutions. There are no perfect solutions. The best that can be offered are solutions that come from a team of experienced people.

I suggest rewriting this question in the reverse. "How did your desired career path affect the education you sought?"

Always start from the point of view that you need more knowledge to understand a problem. Stephen Covey said it best, "seek first to understand, then to be understood."

Everyone has a reason to feel the way they do. Sometimes the expressions that offend the most are just symptoms of the bigger problem. My education has taught me to try and understand the bigger picture and not get plagued by the emotion of it all. Solving problems sometimes requires leaders to endure difficult conversations and circumstances to bring about an acceptable solution. The many aspects of my education have allowed me to be where I am today. Just where I want to be.

What are some key leadership lessons you have learned?
RLJ: Emotional preparedness is imperative. In every situation do your best to understand who you are in a discussion with. Are you teaching individuals who are going through a developmental process, are you working with peers with equivalent responsibilities, or in a discussion with a mentor and should be spending time learning?

Listen, learn, and then lead.

What would you recommend to new graduate therapists just beginning their career?
RLJ: Take a good accountability of what you don't know. It's vast and as you learn more it's like peering over the mountain to see the limitless valley on the other side. Learn everything you can. Everything is your job. From making adjustments on the mechanical ventilator to helping clean a room just after a code. Always be respectful and have some understanding of how the words you are using will be received. Will they portray the correct sentiment or are you responding in the heat of a moment?

Never allow yourself to be put in a position where you must say I don't know what the next step is. Even if that next step is "I need to do some additional reading." Your patients and other caregivers depend on your knowledge. Take responsibility for it and work at it every day.

News…continued from page 8
COPD with moderate PH was defined as mPAP 25-34 mm Hg or mPAP of 21-24 mm Hg with pulmonary vascular resistance (PVR) ≥ 3 Wood Units (WU). COPD without PH was defined as a MPAP < 21 mm Hg or mPAP of 21-24 mm Hg with a PVR < 3 WU. Three independent predictive variables were included in the multivariable prediction model for severe PH:

- Systolic pulmonary arterial pressure (sPAP) ≥ 56 mmHg, estimated by echocardiography
- N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma levels ≥ 650 pg/mL
- The ratio of the main pulmonary artery/ascending aorta diameter at the tubular site (PA/Ao-ratio) in chest CT ≥ 0.93

When all three criteria were met — which occurred in one third of the cohort — the specificity of the predictive model was 94.9% and the positive predictive value for severe PH was 93.5%. In fact, the presence of at least one of the criteria (84% of cases) had a sensitivity of 98.2% and most patients with COPD and severe PH could be detected by the recognition of a severe elevation in PAP, investigators noted.

Millions of Siemens Healthineers Rapid COVID-19 Antigen Self-Tests Now Available in the US
Siemens Healthineers announced the CLINITEST Rapid COVID-19 Antigen Self-Test is now available in the US to self-test for the SARS-CoV-2 virus. The CLINITEST Rapid COVID-19 Antigen Self-Test uses a simple nasal swab to provide accurate COVID-19 test results (including for both the Omicron and Delta variants) in 15 minutes and comes in a five-test-per-box configuration — convenient for families, group, and/or serial testing needs. The test is approved for unsupervised self-testing by individuals ages 14 and older, and adult-collected samples from individuals ages 2-13, with or without symptoms. "Siemens Healthineers is bringing millions of rapid COVID-19 antigen tests to the United States to make them available to the American people at a time when the tests are desperately needed," said Jennifer Zinn, Executive Vice President and Head of Diagnostics, North America, Siemens Healthineers. "Since receiving Emergency Use Authorization for the CLINITEST Rapid COVID-19 Antigen Self-Test in December, we've worked tirelessly to leverage every pathway to bring the tests to the public as quickly as possible. This is in addition to the tremendous efforts we've successfully undertaken to make these tests widely available in Europe." The company has been selected as a test supplier to support the US federal government's efforts to ship tests directly to households. Siemens Healthineers committed to making tens of millions of tests available for the federal government over the next two months. Additionally, Siemens Healthineers is supplying millions more tests for state government programs and to nonprofit organizations. Siemens Healthineers also is supplying the antigen tests to healthcare institutions across the country to ensure front-line workers can continue to care for patients safely. "As Americans struggle to access COVID-19 tests amidst the latest surge, we were eager to step in to help workers and students be safe," said Randi Weingarten, President, American Federation of Teachers. "Working with Siemens Healthineers we are helping educators and school staff, as well as nurses and others we represent, get the supplies they need to keep themselves, their families, and their students safe. Rapid tests provide the peace of mind necessary for our nation's schools to remain safely in person — where students do best — without risking the spread of COVID. Pandemic safety remains a community-wide effort,
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Blood Loss in the NICU: The Difficulty and Tradeoffs of Caring for the Most Fragile Patients

Providing the best care for the most fragile NICU patients is full of challenges and tradeoffs. Sometimes the information doctors need to gather from their patients comes at a cost. When neonatal care teams need to assess how a patient is responding to the current level of ventilatory support, a blood draw is traditionally required. However, that blood draw can contribute to blood loss, pain, and infection risk for the infant.

Why do we need to ventilate NICU patients?

Caring for preterm infants requires 1) ventilating their underdeveloped lungs and 2) protecting their brains — which often have immature blood flow regulation — from intraventricular hemorrhage and other complications.

To determine whether or not the ventilation support that these patients are receiving is adequate, clinicians need to frequently measure and monitor the amount of indicative substances in the blood. One of the most critical is carbon dioxide (CO_2).

CO_2 levels can change quickly in neonates, and monitoring them is important because values too high (hypercarbia) or too low (hypocarbia), as well as fluctuations or sharp changes, have all been linked to intraventricular hemorrhage[1], which happens in as many as 25[2]-42%[3] of neonates weighing less than 1500g at birth.

If ensuring CO_2 remains in a safe range helps support better outcomes for NICU patients, CO_2 levels must be measured and monitored closely.

How do we measure carbon dioxide levels in NICU patients' blood?

The gold standard for measuring CO_2 is through blood draws; Arterial Blood Gases (ABG) and capillary heel sticks are common in the NICU.

These blood samples, although accurate, offer only a point-in-time measurement and can miss periods of elevated or reduced levels of CO_2 in the blood. They also present an infection risk, cause pain and stimulation, and introduce iatrogenic blood loss: blood loss caused by medical examination or treatment.

Why is iatrogenic blood loss important?

We may not typically consider blood draws and heel sticks to be a large driver of patients losing blood, but the issue carries greater significance with neonatal patients, who don't have much blood to give in the first place. One study found that 30% of the circulating blood volume of neonates was drawn for lab work each week in their first six weeks of life.[4]

The significance of this blood loss in the NICU cannot be understated. As another study noted, "to further place this in perspective, 6-7 mL of blood drawn from an infant weighing 1 kg is equivalent to a 450 mL blood loss in an adult."[5] 450 ml is roughly one pint.

If blood loss is so important, why do we draw it so frequently?

The answer, as studies have shown, is often to determine blood gases and pH levels, as well as some electrolytes, all stemming from the desire to monitor how patients are responding to treatment and/or their current level of ventilatory support.

One analysis saw that Very Low Birth Weight (VLBW) infants receive an average of nearly 57 blood gas measurements over the course of, roughly, one week.[6] The unfortunate reality of what happens next is that up to 63% of the blood lost by the infant is wasted.[4]

Transfusion, phlebotomy, and other issues with blood draws

Phlebotomy is well-established as the main nonphysiologic driver of anemia of prematurity,[5] shown through the direct relationship and high correlation values between the volume of blood drawn and the volume of blood transfused.[5,7]

We know that blood taken in these fragile patients must eventually be replaced. Transfusion, however, presents a wide variety of risks and complications in neonates, including infection, vascular overload, lung injury, and sensitization,[8] and has even been linked to increased mortality in adult surgical patients.[9,10]

Transfusion has a complex relationship to Necrotizing Enterocolitis (NEC), with one meta-analysis showing transfusion doubling the risk of developing the condition,[11] and another stating "incidence of Transfusion-associated Necrotizing Enterocolitis varies from 20-35% of NEC cases and reports suggest that infants with TANEC are more likely to develop more surgical NEC."[12]

Patients with transfusion-associated NEC (TANEC) generally have higher mortality, longer hospital stays, and are more likely

to require surgery than non-transfusion NEC patients.[11] Some evidence has even connected transfusions with worsening intraventricular hemorrhages.[13]

Care teams in the NICU need the information that blood draws can deliver, but the cost of iatrogenic blood loss and other risks associated with those draws needs to be fully understood and weighed by the clinician.

How can we reduce blood loss in the NICU?

While this may paint a bleak picture, there are options and strategies for better blood management in the NICU — and small changes can have a big impact for these fragile patients.

In a study in the Journal of Maternal-Fetal and Neonatal Medicine, Clare E Counsilman and colleagues at Leiden University Medical Centre share strategies they've implemented to reduce iatrogenic blood loss in their NICU, such as using placental and umbilical cord blood to decrease blood loss on Day 1 of life and adopting transcutaneous CO2 monitoring to minimize the frequency of blood draws.

Their study concluded that "extreme preterm infants lose almost one-third of their total blood volume in the first month of life as a result of blood loss due to multiple blood draws for laboratory investigations and procedures."

Additionally, Counsilman et al. determined that "in-line point-of-care testing through arterial catheters…or transcutaneous CO_2 measurement might help to reduce the high blood loss associated with mechanical ventilation."

The role of transcutaneous CO_2

Transcutaneous monitors enable non-invasive measurement of patients' CO_2 levels, lessening the need for frequent blood draws without sacrificing visibility to this critical parameter.[14] Although blood draws provide crucial information and will likely never be eliminated from the NICU, efforts to reduce unnecessary blood loss are in the patient's best interest and are already underway in NICUs around the world.

As Counsilman et al. stated in their study, "decreasing the frequency and amount of phlebotomy loss is probably the area in the field of neonatology that can be changed the quickest. This will automatically decrease the risk of neonatal anemia and save substantial transfusions and complications."

Submitted by Sentec. For more information about transcutaneous monitoring, contact sentec.com.

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Utilizing Clinical Data to Enable Better Ventilation Management

Kathryn Clark, RRT-NPS and Howard Brick

For more than a century, neonates have received respiratory support in various modes, including oxygen therapy and ventilation. Since its inception, clinicians have learned a lot from neonates' response to oxygen treatment—both positive and negative. Despite its long tenure in the NICU, it remains a point of contention.[1] Unlike most drugs, oxygen does not have clear guidelines for use, making it difficult to administer therapeutically, especially in the treatment of one of the most fragile and vulnerable patient populations.[2] Mechanical ventilation (MV) can be a lifesaving intervention, but when not closely monitored, there is a risk for injury to the lungs, brain, and other organ systems.[3]

If properly managed, we believe the benefits of ventilation in neonates far outweigh the risks.

The use of oxygen treatment is vital for neonates with various respiratory issues, including Chronic Lung Disease (CLD)/ Bronchopulmonary Dysplasia (BPD), Respiratory Distress Syndrome RDS), and Persistent Pulmonary Hypertension of the Newborn (PPHN). When proper ventilation is used and closely monitored, neonates may benefit from decreased time on a ventilator, resulting in a shorter stay in the NICU.

Kathryn Clark is the Director of Clinical Development at Etiometry. She is the Lead Clinical Specialist at Etiometry and has a decade of experience in critical care procedures, training clinicians, and award-winning clinical research. She is responsible for developing, coordinating, and implementing Etiometry's FDA cleared analytics into clinical workflows worldwide. Prior to Etiometry, she worked with hospital leadership to establish clinical practices, policies, and protocols for the opening of Sidra Medicine in Qatar. Ms. Clark's experience spans across pediatric, adult, and cardiac patients at Boston Children's Hospital, Tampa General, and beyond. Howard Brick is the Chief Strategy Officer at Etiometry. Howard joined Etiometry in 2021 as Chief Strategy Officer, bringing over 20 years of experience in healthcare technology-related information and analytics companies in a variety of executive, commercial, and corporate development roles. Before joining Etiometry, Howard consulted to and advised medical technology and digital health companies on strategic partnering, financing, and go-to market strategies. Prior roles included SVP of Business Development for Senscio Systems, Managing Director at Ferghana Partners and Managing Director, COO and then CEO of MedPanel, a market intelligence provider to the life sciences industry and to life sciences-focused investors. Prior to his career in the healthcare vertical, he worked in mortgage banking analytics and practiced law in Boston. Howard holds a B.A. from Dartmouth College and a J.D. from Columbia University Law School.

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At Etiometry, we are acutely aware of the complex nature of neonatal oxygen therapy. And we sympathize with NICU clinicians who need to achieve a flawless balance between reaching adequate tissue oxygenation and avoiding oxygen toxicity—quite a complex and dangerous challenge. Not to mention, each patient is unique, with individual needs and responsive ranges, so there is no one-size-fits-all solution. For these reasons, the Etiometry R&D team has extensively studied how we can apply our analytics-driven clinical decision-support software to ventilation management in the NICU. Our comprehensive, data-based solution can help clinicians fine-tune ventilation management, analyze risks, and make near real-time decisions to improve outcomes for their patients.

Our platform is an end-to-end data management software solution for the collection, analysis, visualization, and archiving of ICU clinical data. When applied to ventilation management in the NICU, it could facilitate the use of all available data to support the anticipation and management of respiratory disease in neonates. In addition, we can implement our Clinical Management Applications (Clinical MAPs) that guide clinicians through each step of the appropriate protocol process and provides continuous visibility into patients' progress. From identifying eligible patients to assessing protocol performance, these Clinical MAPs automate a hospital's guidelines to improve efficiency and compliance.

As a leader in clinical decision-support software, the Etiometry platform is already utilized in more than 20 of the top children's hospitals nationwide. Clinicians utilizing the platform are able

to better manage patient data to discern actionable information in intensive care settings. We look forward to helping a current or future partner empower their clinicians with the proper technology, process, and protocols for better ventilation outcomes.

About Etiometry

Etiometry Inc. is the leader in clinical decision-support software for the intensive care environment. Our technologies provide valuable clinical insight and analysis to support early recognition of subtle changes in patient condition to avoid complications and speed recovery. Etiometry is committed to improving patient outcomes, increasing clinical efficiency, and lowering costs of care through the more effective use of all available data.

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and with this critical inventory and partnership from Siemens Healthineers, we can help get more tests into the hands of people who need them most."

Masimo Adds Telehealth to Its SafetyNet Telemonitoring System

Masimo announced a major expansion of Masimo SafetyNet that brings robust, secure video conferencing to the remote patient management and connectivity platform to offer a comprehensive telehealth and telemonitoring solution — and for patients, a better "hospital at home" experience. Now, Masimo SafetyNet allows clinicians and hospitals to schedule and conduct multi-way audio- and video-based virtual appointments with at-home patients through the Masimo SafetyNet smartphone app — while still viewing continuous and spot-check vital signs and other physiological data. By combining the power of advanced remote patient monitoring, including Masimo's clinically proven SET pulse oximetry technology, with telemedicine capabilities like virtual visits and the benefits of Masimo's Hospital Automation platform, such as full two-way integration with hospital electronic medical records (EMRs), Masimo SafetyNet enables use of telehealth: the ability to provide full-featured remote care with virtual face-to-face meetings while simultaneously accessing a patient's continuous physiological data. Masimo has integrated TODA, a robust audio and video transcoding technology from LMLabs, to expand Masimo SafetyNet beyond its original remote patient management capabilities. The integrated video solution dynamically adjusts bit rates based on the available bandwidth to transcode live, secure audio and video and ensure the highest quality reproduction with dramatically less required bandwidth. For clinicians, this means they get the best quality virtual visit combined with real-time patient data, no matter where the patient is. Not only are clinicians able to communicate with their patients, but also collaborate with them with the ability to share their screen, launch a digital whiteboard, chat via in-app secure messaging, or invite additional clinicians for more expertise. For patients, Masimo SafetyNet is now the easiest way to connect with their doctors and care team without having to download additional apps or send in their physiological measurements separately. Their virtual visits are conducted through the same smartphone app that collects their oxygen saturation, pulse rate, respiration rate, temperature, and other data from tetherless Masimo Radius PPG and Radius T^{o} sensors. Through the new virtual whiteboard, providers can educate and share additional information as part of the discussion, enriching patient-clinician interactions and allowing them to be tailored to meet each patient's health and communication needs. The integrated messaging feature offers yet another way for patients to stay in touch with their care teams, when a full video consultation is not needed. Joe Kiani, Founder and CEO of Masimo, said, "Masimo SafetyNet has been helping clinicians save and improve patients' lives at home and in the hospital, around the world, since the start of the pandemic. With the addition of advanced telehealth capabilities, our already powerful remote monitoring solution becomes an even more comprehensive platform." Designed to help providers remotely manage patient care, Masimo SafetyNet is a secure, scalable, cloud-based patient management platform that features clinical-grade spot-checking and continuous measurements, CarePrograms (customizable digital care plans), remote patient surveillance, and flexible, automated, two-way integration with hospital EMR systems — now augmented with video telemedicine. First developed for use during the COVID

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Keep it Clean: Improving Oral Hygiene Practices Improves Respiratory Care

Tiffany Oakes, MS, CCC-SLP

Routine oral care interventions reduce bacteria within the oral cavity and on the mucosal membranes and dentition, reducing the risk that bacteria may be mixed with food, liquids, or saliva and misdirected into the airway during the swallow. Not only does poor oral hygiene contribute to risk, but it may be the most common sequelae in aged persons for the risk of aspiration pneumonia.[1] Surveys of patients also revealed that oral care routines and maintaining a healthier oral environment have been related to a greater sense of self-worth.[2] Regular oral hygiene may improve patient comfort and may also help prevent xerostomia, which may be related to mouth-breathing, an open-mouth posture, or a side effect of various medications.[3]

The responsibility of oral hygiene for patients within a facility is interdisciplinary. Not only is oral hygiene a significant factor in disease processes, it also may have a causative component. With poor oral hygiene, periodontal disease becomes a higher risk factor and periodontal disease is associated with cardiovascular disease, stroke, pulmonary disease, diabetes, and other systemic conditions.[4] To provide comprehensive care, oral hygiene becomes a must, and the interdisciplinary collaboration is key.

Who is at risk?

Poor oral care has been identified as predictor of aspiration pneumonia in patients with dysphagia. Additionally, dependence on others for oral care provision places a patient at higher risk for aspiration pneumonia.[5] Older patients, patients with a decreased level of consciousness, and patients with decreased mobility or who are laying supine throughout the day also have an increased risk.[6]

It is important that all patients be screened for oral health status to assist in identifying patients who are at a higher risk of developing hospital-acquired aspiration pneumonia. Research has determined that screening protocols, such as the Oral Health Assessment Tool, are both valid and reliable when used by nursing and allied health clinicians.[7] An initial screening can also provide baseline information for comparison as subsequent oral care treatments and assessments are performed.

Sample components of an oral health screen include assessing:

- Quality and quantity of oral secretions.
- Condition of oral mucosa.
- Appearance of the lips.
- Condition of dentition:
  - Presence of dentures (and fit).
  - Broken, missing, or decayed teeth.
- Appearance and mobility of the tongue.
- Signs of lesions, ulcers, or redness.
- Signs of infection or injury.
- Presence of any residue.
- Level of dependence for performing care.

Endotracheal Intubation

Patients who receive mechanical ventilation via endotracheal intubation experience a reduction in their ability to resist the

Tiffany has been a medical SLP in various settings from acute care to home health, treating both the adult and medically complex pediatric populations. Tiffany has experience developing patient care pathways to guide assessment and treatment selection for patients in home health, at both the state and national level. Currently, she is a full-time Clinical Specialist for Passy-Muir and works with multi-media educational development and presents on topics related to tracheostomies and speaking valves regularly.

colonization of harmful microorganisms in the oral cavity. This may be due to prolonged mouth opening, which reduces the flow of saliva, and placement of the endotracheal tube. The obstruction caused by the endotracheal tube itself hinders accessibility for oral care, allowing for the buildup of a resistant oral biofilm. The endotracheal tube may then serve as a vehicle for the transportation of harmful bacteria from the oral cavity to the lungs. Even with the inflated cuff, microaspirations may occur and contribute to the development of ventilator-associated pneumonia (VAP).[6] Research has shown that providing effective oral care may result in a lower incidence of VAP, reduced requirement for mechanical ventilation, shorter ICU stays, and lower mortality.[8]

Tracheostomy

The timing of the decision to tracheostomize following endotracheal intubation may also impact a patient's oral health. A tracheostomy allows better access to the oral cavity for improved oral hygiene, requires less sedation, and allows for the possibility of oral intake, which may improve the oral environment. Additionally, deflating the tracheostomy tube cuff and placing a Passy-Muir® Valve restores airflow through the nose and mouth and improves management and expectoration of saliva and secretions, which may assist in the maintenance of a healthy oral environment.

NPO

Patients with an endotracheal tube are nil per os (NPO), meaning nothing by mouth, as are many patients with tracheostomy prior to a swallowing assessment. Patients who are NPO typically receive, either temporarily or permanently, nutrition via nasogastric or gastrostomy tube. These patients are at an even higher risk of aspirating oral pathogens than patients who are fed orally. This may be due to a reported decrease in the amount of attention paid to the oral cavities of patients who are not receiving an oral diet.[9] These patients can and should be receiving regular oral care. A cleaner oral environment would not only decrease the risk of aspiration of respiratory pathogens and improve the oral environment but may also allow the patient to better participate in dysphagia (swallowing disorders) therapy. While not standardized for patients with tracheostomy, often the Frazier Free Water Protocol and the Ice Chip Protocol are used with this patient population, and both require thorough oral care prior to initiation.[10-11]

So, what's the problem?

Though the research to support the benefits of oral care exists across multiple studies, diagnoses, and medical settings, oral hygiene is often not provided unless there is a standardized protocol in place. Research has investigated a knowledge gap that exists between understanding the importance of oral care and actually performing oral care tasks for patients.[12-13]

Pettit et al. (2012) surveyed a random sample of registered nurses using a mailed questionnaire that assessed oral care knowledge, practices, perceptions of importance, and barriers to providing oral care.[14] While a large majority of respondents, reported they believed oral care was important (95%) and felt responsible for providing oral care (79%), over half (52%) admitted oral care was addressed only minimally in their nursing education and training. Reported barriers to performing oral care included, low priority, lack of time, lack of resources, and no employer mandate.

Common barriers to oral care have been reported as:

- Lack of staff education and training.
- Limited availability of or access to supplies.
- Unknown roles and responsibilities.
- Lack of protocol.
- Time constraints.
- Documentation issues.
- Lower priority of patient care tasks.
- Staffing issues.

While much of the research on and perceived responsibility of oral hygiene focuses on nurses and nursing staff; however, it is important to understand that all members of the interdisciplinary team play an important role in the development and routine practice of better oral care protocols. Having an interdisciplinary approach will further improve compliance and lead to improved patient comfort and a decreased risk of aspiration of oral bacteria, a potential contributor to the development of acquired pneumonia.[9]

Developing a protocol

Education and training are a great place to start with implementing a successful oral care protocol. At all levels of care and in all healthcare settings, clinicians, patients, and patients' caregivers should be educated on the importance of oral care, the risks of poor oral hygiene, and how and when to perform oral care.

Sample staff training interventions include:

- Providing in-services training.
- Demonstration videos.
- Hands-on demonstration.
- Skills lab.
- Competency checklist.
- Defining roles and responsibilities.
- Benefits training.
- Assessment and routine documentation.

Wennerholm et al. (2021) detailed a facility's development of a multidisciplinary Oral Care Task Force to improve the provision of oral care.[15] This facility screened patients and placed them into one of four categories based on needs. They developed oral care kits based on those categories of patient need and made them easily available to staff or patients if patients were deemed independent. The task force focused

on e-learning and hands-on demonstrations for performing oral care with a standardized protocol and developed a documentation template in the electronic medical record to aid in ease and compliance of documentation. They determined that while this project was challenging, it was feasible and successful to lower the rate of hospital-acquired aspiration pneumonia.[15]

Another study found that by increasing the supply and availability of oral care tools and creating a standardized placement of those tools in the patients' rooms, oral hygiene for patients receiving mechanical ventilation improved significantly.[16] They reported that having a standardized oral hygiene placement protocol in the patient's room significantly improved staff compliance and patient outcomes.

Oral care kits should be kept at the patient bedside for ease of access and use. Even patients who are deemed independent in performing oral care or have available caregivers may benefit from ease of access to supplies, education, and encouragement to perform oral care.

Sample oral care kit supplies include:
- Toothbrush (suction toothbrush).
- Toothpaste (consider non-foaming).
- Oral swabs.
- Distilled water.
- Oral antiseptic.
- Clean cloth, gauze, or wipe.
- Basin.
- Lip balm (mouth moisturizer).
- Denture cleaner, if needed.
- Denture adhesive, if needed.

Patients should receive or perform oral care at least 2–3 times daily and prior to any oral intake. Using it prior to oral intake decreases the presence of oral bacteria that may be misdirected toward the airway during the swallow. If a patient wears dentures, they should also be cleaned, in addition to the performance of regular oral hygiene. It is important that the dentures be completely removed for proper cleaning of the gums and palate.

Summary

A simply written step-by-step protocol for patients at each level of care has been shown to improve patient outcomes, increase provision of oral care services, and reduce healthcare costs.[17] An interdisciplinary approach to identifying and providing oral care has been shown to improve patient outcomes.[15] Each member of the team should be trained and aware of the oral health of their patients. Having a more consistent level of awareness with proper training enhances patient quality of life and medical care, while also reducing the risks associated with various disease processes and hospital-acquired aspiration pneumonia.

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pandemic, for lower-acuity patients recovering or quarantining at home, Masimo SafetyNet has expanded use to post-surgical patients, patients with a variety of chronic conditions, and to patients with episodic illnesses, including fever. The platform helps seamlessly extend care from the hospital to the home (or any other location outside of the hospital or doctor's office) by collecting monitoring data from the fingertip and chest-worn sensors, relayed to the patient's smartphone with Bluetooth®, and from there to the secure Masimo SafetyNet cloud. Using the web-based clinician portal, doctors and other clinicians can keep an eye on patients' physiological progress from afar, intervening if a patient's condition appears to worsen, and now with the ability to conduct comprehensive virtual visits as well.

Vitalograph announces the much-anticipated arrival of the new Alpha Spirometer

Vitalograph has announced that their highly portable, lightweight, all-in-one desktop spirometer and printer is now available in the USA. The next-generation Alpha Spirometer, with integrated printer, is a lightweight and durable tool for accurate respiratory diagnosis of both adults and pediatrics. Capture reliable test results immediately with Alpha's Fleisch measuring technology, which is extremely accurate and stable over time. Designed for testing on the go, remotely, or in a clinic, the Alpha is the ultimate desktop spirometry solution. Crucially, compliance with the 2019 ATS/ERS spirometry guidelines ensures that all respiratory diagnostics carried out are in line with international standards for accuracy and reporting. Vitalograph's Executive Vice President of Sales & Operations for North America, Troy Pridgeon said: "It is very exciting and great timing to have another next generation product available just as many healthcare sites are looking to reopen spirometry testing in the wake of the pandemic. COVID has kept patients with lung diseases and those that work around known respiratory hazards untested for as long as two years in some cases. The Alpha is a great solution to catch that up and help ensure that one health crisis doesn't create another."

Simple Screening Tools Could Help Identify COPD in Low-, Middle-Income Countries

Undiagnosed but clinically significant chronic obstructive pulmonary disease (COPD) may be widespread in many low- and middle-income countries, according to a large international study led by researchers at University College London (UCL). But the study found that a short questionnaire combined with peak expiratory flow provides a simple and cost-effective way to identify people at high risk of COPD in these settings. COPD, including emphysema and chronic bronchitis, affects more than 300 million people globally. It is the third leading cause of mortality worldwide, with around 3 million deaths from COPD each year. However the burden of chronic lung disease is not shared equally around the world. Around 90% of deaths from COPD occur in low- and middle-income countries. Globally COPD is also a major risk factor for poorer COVID-19 outcomes. Professor John Hurst, principal investigator on the study, said: "In contrast to studies in high-income settings, our results suggest that screening for COPD in low- and middle-income countries finds undiagnosed, yet clinically significant disease — arguing for a more proactive approach to respiratory care.

"Our findings support the accuracy and feasibility of using simple screening tools to identify people affected by COPD living
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The Role of Noninvasive Ventilation in Neuromuscular Disorders

A summary of highlights from presentations at the 1st Respiratory Failure and Mechanical Ventilation Conference 2020 by Wolfram Windisch (Cologne, Germany), Anita Simonds (London, United Kingdom) and Peter Wijkstra (Groningen, Netherlands)

Chris Campbell

Pulmonary comorbidities, including chronic obstructive pulmonary disease (COPD), asthma and congestive heart failure, are frequently found in adults with neuromuscular diseases (NMD), particularly those with rapidly progressive disease such as motor neurone disease or amyotrophic lateral sclerosis (ALS).[1] As a result, healthcare utilisation for pulmonary complications is substantial, and depends on the age of the patient, with a higher frequency in those aged over 70 years. In a population study, more than one-third of adults with neuromuscular disease had undergone pulmonary outpatient clinic visits with a mean 6 visits per patients, pulmonary function testing in about a third, sleep studies in 14% and 16% having intensive care unit (ICU) admissions. There were disparities according to income level, and only a minority received ventilatory support. In patients with ALS, 6% received home mechanical ventilation (HMV).[1] Blood gases and lung function parameters vary substantially between patients with differing neuromuscular disorders when started on HMV: patients with ALS are very likely to have HMV but are typically referred late in the disease, compared with Duchenne muscular dystrophy (DMD) patients who tend to receive HMV earlier in the disease course.[2]

When considering the benefits of artificial ventilation, it is important to remember that the respiratory system consists of two components: the lungs and respiratory pump. Pulmonary failure leads to hypoxaemic respiratory failure, whereas pump insufficiency and ventilatory failure lead to hypercapnic respiratory failure. Oxygen therapy is not indicated in the latter scenario; artificial ventilation is needed. The management of respiratory failure in NMD requires the use of artificial ventilation to assist the respiratory muscles in order to correct the alveolar hypoventilation and ameliorate gas exchange.

The benefits of artificial ventilation were first demonstrated in 1953 during a polio epidemic, when the use of 24 hour manual ventilation caused mortality to plummet from 92 to 25%.[3] Since then, a wide range of NMD have been found to benefit from artificial ventilation, primarily by noninvasive ventilation (NIV). National guidelines have algorithms recommending when patients should be referred and offered NIV. German guidelines recommend considering NIV when patients are symptomatic, there is evidence of respiratory muscle weakness or forced vital capacity (FVC) falls below 70% of the predicted value. The decision should be individually tailored but it is important to start early when patients start to become hypercapnic.[4] Improved survival with NIV has been demonstrated in patients with progressive NMD, and also in some subgroups of patients with COPD, suggesting that the effect is NIV is not limited to the respiratory pump.[5] In hypercapnic patients with DMD, NIV has a substantial impact on long term survival.[6] Other neuromuscular conditions include where NIV may be used include spinal muscular atrophy (SMA), X-linked myotubular myopathy, congenital muscular dystrophy and mitochondrial disorders.

Deciding when to initiate NIV can present challenges in patients with rapidly progressing NMD. It can be difficult to predict how quickly a disease is going to progress in a newly diagnosed person with ALS. Patients can be broadly categorised as rapidly progressive or less rapidly progressive but the decision can be difficult on an individual basis. Younger age at diagnosis, delay between symptom onset and diagnosis, and FVC are useful prognostic factors for respiratory insufficiency in ALS.[7] A recent study showed that the decline in vital capacity was rapid at first but slowed after about 17 months.[8] The introduction of NIV in childhood is associated with an increase in survival in a range of progressive conditions,[9] and has a favourable long-term impact on nocturnal and diurnal gas exchange.[10]

Identifying biomarkers of disease progression would be useful to inform treatment decisions. A randomised controlled trial in patients with ALS found that NIV improved survival in the subgroup of patients with mild/moderate bulbar weakness on study entrance. In patients with severe bulbar impairment, NIV improved sleep- related symptoms, but did not confer a large survival advantage.[11] Sleep disordered breathing, particularly nocturnal hypoventilation (NH) is a complication of respiratory involvement in NMD that can evolve into symptomatic daytime hypercapnia if not treated with NIV.[12] Respiratory polygraphy is generally used to detect NH; oxycapnography may also be used. Paediatric patients with NMD can develop NH in the absence of clinical symptoms or other signs of nocturnal altered gas exchange. Monitoring of nocturnal hypoventilation should, therefore, be included among nocturnal respiratory assessments of these patients as an additional tool to determine when to initiate NIV.[13]

Cough is impaired in NMD and therefore cough assisting is an important part of the management of the condition. Inspiratory weakness leads to a reduction of inspiratory volume, bulbar weakness impairs the glottis closure and expiratory weakness reduces cough pressure. Maximum insufflation capacity (MIC)

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and peak cough flow (PCF) should be measured at each clinic. The latter is most important in terms of deciding when to start treatment. Peak cough flow should be 360–840 L/min. In clinical practice, a PCF between 160 and 200 L/min is considered an effective cough.

Airway clearance techniques include cough augmentation (assisted inspiration/expiration) and sputum mobilisation.[14] Manually assisted coughing and mechanical insufflation/ exufflation (MI-E) are effective and safe methods for clearing airway secretion in patients with NMD.[15] Breath stacking or airstacking with a mask and one way valve can achieve significantly increased lung volumes in NMD patients.[16,17]

In weaker patients, MI-E is the most appropriate choice. It has been shown to increase PCF, reduce dyspnoea and reduce the duration of the session, which is important for the patient.[18] It has also been found to be beneficial in NMD patients with upper respiratory tract infections.[19] It is important that inspiratory and expiratory timing/ pressures are individualized. Patients with ALS are likely to benefit from lower pressures, triggered insufflation and longer insufflation time. Greater exsufflation pressures than insufflation pressures, together with a shorter insufflation time than exsufflation time, should be used. Subjects who produced daily secretions are more likely to use MI-E every day.[20]

The use of MI-E is not supported by a strong body of clinical trial evidence; a 2013 Cochrane review found that only 5 studies with a total of 105 participants were eligible for inclusion, and concluded that there was insufficient evidence for or against the use of MI-E in people with NMD.[21] But despite the lack of evidence, experts consider that it must be used in weak patients with NMD.

In summary, this summary has demonstrated that management of respiratory failure in patients with NMD requires the use of NIV and that the management of cough impairment in weak patients requires MI-E. As patients with some NMDs are living longer, long term consequences of these interventions will arise; Clinical experience shows older patients now experiencing new, and some potentially fatal, complications of NIV. Further research is needed on how best to address these.

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in diverse low- and middle-income settings." In high-income countries, COPD can be readily diagnosed using spirometry. The main risk factor for COPD in this population is smoking, and screen-detected disease is usually mild or moderate. In poorer countries the situation is more complex. Additional risk factors include smoke from biomass fuels used for cooking or heating, and poverty-associated factors such as impaired lung development and tuberculosis. Yet spirometry remains impractical as a screening tool in many resource-poor areas because of the need for equipment, training, and interpretation from skilled personnel. More cost-effective screening tools are needed in these settings to identify people who require further confirmatory testing.

Volunteers Needed to Catch COVID in the Name of Science

The world's first medical trial authorised to deliberately expose participants to the coronavirus is seeking more volunteers as it steps up efforts to help develop better vaccines. The Oxford University trial was launched last April, three months after Britain became the first country to approve what are known as challenge trials for humans involving COVID-19. Its first phase, still ongoing, has focused on finding out how much of the virus is needed to trigger an infection while the second will aim to determine the immune response needed to ward one off, the university said in a statement. Researchers are close to establishing the weakest possible virus infection that assures about half of people exposed to it get asymptomatic or mild COVID-19. They then plan to expose volunteers - all previously naturally infected or vaccinated - to that dose of the virus's original variant to determine what levels of antibodies or immune T-cells are required to prevent an infection. "This is the immune response we then need to induce with a new vaccine," said Helen McShane, Oxford University Professor of Vaccinology and the study's chief investigator. The trial's findings will help make future vaccine development much quicker and more efficient, the statement said.

US FDA Labels Philips' Expanded Ventilator Recall as Most Serious

The US Food and Drug Administration (FDA) on Wednesday classified an expanded recall of certain ventilators by Philips (PHG.AS) late last year as Class 1, or the most serious type, saying they could lead to injuries or death. The Dutch medical equipment company initiated the recall of 215 Trilogy Evo ventilators and 51 repair kits in the United States due to potential health risks from a type of foam used in the devices. So far, there have been no reported injuries or deaths from the products, which were distributed in the United States and Korea, the FDA said. "We have already reached the majority of affected customers and we will correct this issue via a repair (replacement of the foam) on site in the coming months" a company spokesperson said in an emailed statement to Reuters. This is the latest recall by Philips to be labeled Class 1 after it pulled back up to 4 million breathing-aid machines last year amid concerns that a polyurethane foam used in the devices could degrade and become toxic.

Pneumonia in Infancy Predicts Respiratory Problems in Early Childhood

Preschoolers who experienced community-acquired pneumonia in infancy were significantly more likely than those
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Micro-Preemie Beats Odds to Become Busy Toddler

Unique Cardiac and Respiratory Care for Infants with BPD (CRIB) Program helps patients like Haven thrive

Three-year-old Haven Greyson Smith likes to break odds and set records — whether that's playing at home or surviving despite being given a 10-per-cent chance. With help from his devoted mom and an army of health care professionals, Haven has beaten all odds and expectations as a "micro-preemie."

"It hasn't always been easy, but none of that matters. I have a thriving three-year-old, which I didn't always believe I'd have," Amanda says.

Born at just 25 weeks gestation, Haven earned the title of tiniest baby born at Lucile Packard Children's Hospital Stanford in 2019. Nicknamed 'Tiny Peanut' by the neonatal intensive care unit (NICU) nurses, he weighed just 0.9 pounds at birth. Amanda compared him to the size of a soda can. She likes to say that when he finally left the hospital's NICU after eight months, weighing just over eight pounds, he was "eight times the Haven he was when he was born."

Amanda's high-risk pregnancy was complicated by intrauterine growth restriction, leading to his early delivery. It's common for micro-preemies this small to have challenges such as breathing and feeding problems, and Haven was no exception. The Nest at Packard Children's, which cares for the smallest preemies, has developed specialized ventilator protocols to assist the breathing of micro-preemies to promote a gentle approach and minimize future breathing complications. This approach allowed Haven to finally breathe without ventilator support at six weeks of age and just over two pounds.

Growth-restricted babies are also at risk for developing future lung complications. Lungs are the last organ to develop, so when babies are born prematurely their lungs are not fully formed. This can cause heart-lung problems, and leave kids fatigued and short of breath.

The Packard Children's Cardiac and Respiratory Care for Infants with BPD (CRIB) Program Care Team was established to address complications of prematurity. In 2019, CRIB began monitoring Haven's bronchopulmonary dysplasia (BPD) and pulmonary hypertension as a newborn and continues to do so today.

Doctors at Lucile Packard Children's Hospital Stanford created CRIB because of the constant need for communications between the cardiologists, pulmonologists, and neonatologists who care for preemies who have both lung and heart disease. The coordinated, multidisciplinary effort means convenient, seamless, and exceptional care for highly complex preemies in the hospital and through the years as they grow. While there are other hospitals that have BPD follow-up programs, the true multidisciplinary approach at Stanford Children's Health is what makes CRIB unique.

Haven Greyson Smith has giggling fits, enjoys throwing things, and loves to snuggle on his mom's lap. Photo from 2021 provided by Stanford Children's Health.

"What's great about CRIB is that with pulmonary hypertension you need both a heart doctor and a lung doctor talking and agreeing on treatment, so you get that comprehensive look in one appointment," Amanda says.

This article is contributed by Stanford Children's Health.

Helping Haven go home

"Each lung has an array of blood vessels, shaped like a tree. When a baby is born early, this vascular tree is like a tree in winter. It's missing all its little branches and the leaves in between," says Rachel Hopper, MD, pediatric cardiologist at Stanford Children's Health and co-director of CRIB. "This puts pressure on the heart to pump more blood and can cause high blood pressure in the lungs."

Haven's pulmonary hypertension demanded a specialized use of the drug treprostinil, a medication that was delivered 24/7 from a pump that he wore continuously to enhance blood flow in his lungs and make it easier for his heart to pump blood. Without this stress, his body was better able to grow and develop, and Haven transitioned off the drug last year. Treprostinil tends only to be prescribed by large pediatric heart centers with a PH program, like Lucile Packard Children's Hospital Stanford. Amanda credits the medicine for enabling Haven to come home.

"As we support Haven's ability to grow new lung tissue and blood vessels, we are seeing his lungs improve," says Michael Tracy, MD, pediatric pulmonologist at Stanford Children's Health and co-director of CRIB. "Research used to say that lungs became fully developed by age two or three. Now, we are learning that lungs continue to develop even into adolescence."

Stanford Children's Health, with Lucile Packard Children's Hospital Stanford as its center, continues to expand CRIB and research efforts to further improve care for patients with BPD. The team is part of the Pediatric Pulmonary Hypertension Network, a national group of pediatric pulmonary hypertension experts, and the BPD Collaborative, a national group of multidisciplinary care teams dedicated to optimizing outcomes of infants and children with severe BPD. Participation in these organizations empowers doctors to identify trends and improve care. They hope research will eventually lead to novel treatments, like stem cell therapies that could potentially help repair damaged lungs.

"Haven is clearly a fighter, and he's getting more fight in him as he gets older," Dr Tracy says.

To support his heart and lungs, Haven is sometimes hooked up to oxygen at night. A victory was weaning him off oxygen during the day, giving Haven one less cord to tether him.

As Haven grows, so does his lung capacity, making it easier for oxygen to flow and creating less work for his heart. The hope is that he can eventually come off oxygen altogether. In the meantime, Haven is conquering even more milestones—most recently, going to his first day of in-person preschool.

"It's rewarding to care for preemies like Haven. For many the first year can be dicey, especially with pulmonary hypertension," Dr Hopper says. "But we know that if we can get babies to two years of life, many will grow and thrive."

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with no history of pneumonia to develop chronic respiratory disorders, based on data from approximately 7000 individuals. "Lower respiratory tract infections (LRTI) during the first years of life cause injury to the rapidly developing lung at its most critical stage," wrote Rotem Lapidot, MD, of Boston University, Massachusetts, and colleagues. Previous research has linked pneumonia with subsequent chronic cough, bronchitis, and recurrent pneumonia in children, but data are needed to assess the impact of early community-acquired pneumonia (CAP) on respiratory health in otherwise healthy infants, the researchers said. In a retrospective matched cohort study published in *Respiratory Medicine*, the researchers identified 1343 infants who had CAP in the first 2 years of life, and 6715 controls using a large electronic health records dataset (Optum EHR dataset) for the period from January 2011 through June 2018. The primary outcomes were the development of any chronic respiratory disorders, reactive airway disease, and CAP hospitalizations between ages 2 and 5 years. Infants in the CAP group were otherwise healthy; those with congenital or other conditions that might predispose them to pneumonia were excluded. Baseline characteristics were similar between the CAP patients and controls. Overall, the rates per 100 patient-years for any chronic respiratory disorder were 11.6 for CAP patients vs 4.9 for controls (relative risk 2.4). Rates for reactive airway disease and CAP hospitalization were 6.1 vs 1.9 per 100 patient-years (RR 3.2) and 1.0 vs 0.2 per 100 patient-years (RR 6.3) for the CAP patients and controls, respectively. The distribution of CAP etiology of CAP in infants at the first hospitalization was 20% bacterial, 27% viral, and 53% unspecified. The relative rates of later respiratory illness were similar across etiologies of the initial hospitalization for CAP, which support the association between infant CAP and later respiratory disease, the researchers said. Nearly all (97%) of the CAP patients had only one qualifying hospitalization for CAP before 2 years of age, and the mean age at the first hospitalization was 8.9 months. "Rates and relative rates of any chronic respiratory disorder, and our composite for reactive airway disease, increased with age at which the initial CAP hospitalization occurred," and were highest for children hospitalized at close to 2 years of age, the researchers noted. "Our findings add to the evolving hypothesis that persistent inflammation following pneumonia creates an increased risk for subsequent respiratory disease and exacerbations of underlying disease," the researchers wrote in their discussion of the findings.

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Long-Term Predictors of Severe Exacerbations and Mortality in a Cohort of Well-Characterized Adults with Asthma

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Abstract

Background: We aimed to explore long-term predictors of severe exacerbations and mortality in adults with well-characterised asthma.

Study design and methods: Adults (aged ≥ 15) with an objectively verified diagnosis of asthma were recruited from a Danish respiratory outpatient clinic between 1974 and 1990. All individuals were followed in Danish registries for vital status, hospital admissions for asthma and cause of death until end of 2017. Predictors of exacerbations were obtained from a repeated measures model. Standardised mortality rates (SMR) for all-causes were compared with the Danish background population. Hazard ratios for mortality were obtained from a cox proportional hazards model in a two-step process.

Results: At baseline, the cohort comprised 1071 patients (mean age 38, SD 16, 61% women), of whom 357 (33%) died during follow-up, with 93 (26%) dying from asthma (primary diagnosis). We found an SMR of 1.24 (95% CI 1.11–1.37, p < 0.001) for all-cause mortality. Baseline predictors for asthma-related death and repeated severe exacerbations were increasing age, ever smoker, FEV1 < 80% pred., high blood eosinophils, longer duration of symptoms and use of SABA > twice daily. Being non-atopic, having a positive histamine challenge test and symptoms more than twice a week were also predictors of repeated exacerbations.

Conclusions: Markers of poor asthma control, including high use of SABA, are predictors of long-term exacerbation rate and mortality over 30 years in patients with well-characterised asthma. Improving asthma control, including lung function and reducing use of reliever medication, is vital for improving the long-term outcome of asthma.

Introduction

Asthma is one of the most common diseases worldwide.[1] Also, asthma places a massive burden due to profound societal and healthcare costs.[2,3]

A multitude of short-term studies, case reviews and national cross-sectional studies have provided us with a good understanding of critical short-term risks for exacerbations and mortality in persons who have asthma. Where age, smoking, poor asthma control, insufficient asthma medication, pulmonary function and lack of follow-up are vital factors.[1,4–6]

Exacerbations present a significant burden on persons with asthma. Exacerbations lead to contact with or admission in the healthcare sector, and in some cases, near-fatal or fatal asthma.[7] Previous studies have found the following factors to be associated with exacerbations,Age, lung function, comorbidities, sputum eosinophils and disease control.[8,9] However, the majority of these studies have a relatively short follow-up. As the severity for individual asthma patients can vary considerably, and there appears to be substantial instability of phenotypes, potentially factors predictive of short-term outcomes may change long-term.[10,11]

Very few cohort studies have reported risk factors for asthma-related mortality.[12,13] The majority of information we have is based on all-cause mortality cohorts or older case-control studies.[5,14–16] Many of the short-term factors also appear to affect long-term all-cause mortality, particularly age, smoking and reduced lung function. However, the long-term consequences and risks for exacerbations and, particularly, asthma-related mortality remain an area ripe for further knowledge.

This long-term Danish asthma cohort study aimed to investigate potential risk factors identified at cohort enrolment for repeated exacerbations, all-cause and asthma-related mortality in adults with well-characterised asthma. Additionally, to investigate the mortality rate in adults with asthma compared with the Danish background population.

Methods

This was a long-term observational cohort study. The cohort has previously been described in Ulrik et al.[17] and Ali et al.[18] The Cohort consists of consecutive persons age 13 or above, referred to the Allergy and Chest Clinic Frederiksberg Hospital, Denmark, between 1974 and 1990. All persons were referred due to known or suspected asthma. The cohort will be referred to as the treatable traits in asthma—impact on long-term outcome (TRAIL) Cohort.

The study was approved by the ethical committee for the Capital Region of Denmark (H-17025043) and The Danish Data Protection Agency (2013-41-2618).

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Table 1 Comparison of baseline characteristics of the TRAIL cohort, between those who experience 0, 1–2 and 3 + exacerbations

	0 (n = 849)	1–2 (n = 182)	3 + (n = 40)	p-value
Sex, n women (%)	506 (60)	114 (63)	29 (73)	0.228
Age	35 (14)	50 (15)	54 (13)	< 0.001
Decade of inclusion				
1974–1979	115 (14)	40 (22)	9 (23)	0.013
1980–1989	641 (76)	131 (72)	27 (68)	
1990	93 (11)	11 (6)	4 (10)	
Adultonset[a], n (%)	587 (69)	147 (81)	33 (83)	0.002
Ever smoker[b], n (%)	283 (33)	74 (41)	22 (55)	0.006
Pack-years[c]	9.7 (8.7)	15 (9.5)	16 (15)	< 0.001
Previous severe exacerbation, n (%)	136 (16)	18 (10)	6 (15)	0.100
Daily symptoms, n (%)	271 (32)	98 (54)	29 (73)	< 0.001
Daily use of β_2-agonist (> 2 puffs), n (%)	399 (47)	120 (66)	32 (80)	< 0.001
High dose ICS or any dose OCS, n (%)	184 (22)	46 (25)	14 (35)	0.096
Lung function				
FEV_1% pred	86 (17)	74 (21)	61 (22)	< 0.001
FVC % pred	94 (15)	87 (17)	78 (16)	< 0.001
FEV_1/FVC ratio	78 (71–82)	70 (58–77)	58 (54–73)	< 0.001
BD reversibility, n (%)				
< 12%	130 (16)	25 (15)	2 (5)	0.221
≥ 12%	688 (84)	145 (85)	35 (95)	
AHR[d]	2.4 (1.7–4.5)	2.1 (1.3–4.6)	2.1 (1.00–3.1)	0.072
Peak flow variability, %	22 (15–29)	22 (13–26)	21 (12–25)	0.200
Blood eosinophils	0.34 (0.21–0.57)	0.38 (0.21–0.57)	0.45 (0.23–0.54)	0.534
Total IgE, IU/l	129 (43–345)	93 (35–317)	125 (33–279)	0.165
Negative skin prick test, n (%)	326 (38)	114 (63)	29 (73)	< 0.001

Data are presented as mean (standard deviation) or median interquartile range), unless otherwise stated

AHR airway hyperresponsiveness, *BD* bronchodilator, *FEV_1* forced expiratory volume in 1 second, *FVC* forced vital capacity, *ICS* inhaled corticosteroids, *IU* International Unit, *OCS* oral corticosteroids

[a] Age ≥ 18 years

[b] Current or ex-smokers

[c] For ever smokers

[d] Missing data on 266

Cohort

The cohort comprised all persons diagnosed with and followed for asthma between 1974 and 1990 at Frederiksberg Respiratory and Allergy Clinic, Denmark. The persons included were≥ 13 years old at baseline. The diagnosis of asthma was made by a specialist in respiratory medicine based on a typical history (wheezing or attacks of breathlessness; chest tightness; cough triggered by exercise, exposure to allergens or irritants or respiratory infections) and at least one of the following:

(1) FEV_1 reversibility > 15% (and an absolute increase of > 150 ml) after a standard dose of short-acting β_2-agonist (SABA), oral corticosteroid or both (30 mg/ day) for 14 days.
(2) Diurnal variability in peak expiratory flow (PEF) rate> 20% and absolute variation> 100 l/min.
(3) Positive histamine provocation test, with the provocative concentration of histamine that results in a 20% drop in FEV_1 (PC_{20}) ≤ 8 mg/ml.

All cut-off values are based on clinical practice at baseline. At the time of referral to the respiratory outpatient clinic, a comprehensive history was obtained. Total serum IgE was determined by paper radio-immunosorbent test (Pharmacia). A skin prick test with standard aeroallergens was performed. The blood eosinophil count was determined three times for each patient, the most abnormal result was recorded. Forced expiratory volume in 1. second (FEV_1) and forced vital capacity (FVC) were measured using a dry-wedge bellows spirometer (Vitalograph). The best of three technically acceptable readings were recorded. The tests were repeated 15 min after inhalation of a standard dose of bronchodilator. Reversibility of FEV_1 was calculated as (FEV_1 after – FEV_1 before)/FEV_1 before). All baseline data were gathered from patient records. All persons went through the same diagnostic algorithm for persons referred for suspected asthma.

Outcomes

Information on hospital admissions and emergency department visits were obtained from the Danish national patient registry. Hospital and emergency department admissions with the primary diagnoses as the following were defined as asthma exacerbation: acute lower respiratory infection (ICD-8: 480–486 and ICD-10: DJ12-18) or chronic airway disease (ICD-8: 490–493 and ICD-10: DJ40–47). A new admission within 14 days of discharge was counted as the same exacerbation.

Table 2 Predictors of repeated asthma exacerbations

	Bivariate model HR (95% CI)	Multivariable model HR (95% CI)
Sex, women	1.17 (0.94–1.46)	–
Age		
15–45	1.00	1.00
46–69	6.00 (4.67–7.71)**	3.56 (2.64–4.81)**
≥ 70	11.2 (7.29–17.2)**	6.30 (3.91–10.1)**
Decade of inclusion		
1974–1979	1.21 (0.76–1.95)	–
1980–1989	1.10 (0.72–1.68)	–
1990	1.00	–
Years since symptom debut	1.02 (1.01–1.03)**	1.02 (1.00–1.03)*
Adult-onset[a]	1.85 (1.41–2.43)**	1.20 (0.81–1.79)
Ever smoker[b]	1.57 (1.19–1.82)**	1.50 (1.20–1.88)*
Pack-years[c]	1.03 (1.02–1.04)**	1.03 (1.01–1.04)*
Previous severe exacerbation	0.68 (0.50–0.94)*	1.27 (0.89–1.82)
Daily symptoms	2.49 (1.98–3.12)**	1.56 (1.22–1.99)*
Daily β_2-agonist usage, > 2	2.2 (1.74–2.78)**	1.50 (1.13–1.98)*
ICS prescribed at baseline, any dose	1.37 (1.08–1.73)*	0.93 (0.72–1.19)
Lung function		
FEV_1 pred. < 80%	3.04 (2.41–3.83)**	1.70 (1.29–2.25)*
FEV_1/FVC ratio, < 70%	2.84 (2.28–3.55) *	1.13 (0.86–1.49)
BD reversibility[d]		
< 12%	–	–
≥ 12%	1.31 (0.96–1.81)	–
AHR, mg/ml		
< 1	1.00	1.90 (0.99–3.67)
≥ 1 to < 2	0.65 (0.44–0.96)*	1.41 (0.72–2.76)
≥ 2 to < 8	0.56 (0.43–0.80)*	1.92 (1.02–3.60)*
≥ 8	1.01 (0.54–1.89)	1.00
Peakflow variability		
< 20%	1.00	–
≥ 20%	0.84 (0.68–1.04)	–
Blood eosinophils, × 10^9/l		
< 0.09	1.31 (0.84–2.04)	0.98 (0.60–1.59)
≥ 0.09 to ≤ 0.4	1.00	1.00
> 0.4	1.33 (1.08–1.65)*	1.29 (1.03–1.61)*
Total IgE, ≥ 150 IU/l	0.71 (0.57–0.89)*	0.99 (0.77–1.27)
Negative skin prick test, n (%)	0.36 (0.28–0.45)**	1.67 (1.25–2.23)*

Results from bivariate and multivariable cox proportional hazards (PWP) model shown as hazard ratio (95% CI)

AHR airway hyperresponsiveness, *BD* bronchodilator, *FEV_1* forced expiratory volume in 1 second, *FVC* forced vital capacity, *ICS* inhaled corticosteroids, *IU* International Unit, *OCS* oral corticosteroids

[a] Age ≥ 18 years

[b] Current or ex-smoker

[c] Only ever-smokers

[d] 46 did not have data

*p-value < 0.05. **p-value < 0.001. Multivariable model: Wald $Chi^2 = 321$ Degrees of freedom = 15. p < 0.0001

All participants were followed from their baseline visit (from 1974 to 1990) and until 31 December 2017. Information about deaths was obtained from the Danish Death Register. Asthma-related death was defined as the cause of death due to acute lower respiratory infection (ICD-8: 480–486 and ICD-10: DJ12-18) or asthma and COPD (ICD-8: 490–493 and ICD-10: DJ40–47). Mortality in the Danish background population was calculated based on data from Statistics Denmark.

Statistics

Differences at baseline were compared using student's t-test, Mann-Whitney U-test and Fisher's exact test. The indirect standardised mortality rate (SMR) for the TRAIL cohort was calculated in comparison to all-cause mortality in the entire Danish population. Mortality rates were stratified by age (0-45, 46-69 and ≥ 70 years) and year of death (1974-1989, 1990-1999 and 2000-2017) to account for differences in mortality across age groups and time. The following factors, recorded at baseline, potentially being predictors of exacerbation and death were examined: Age, decade of inclusion in the cohort, sex, childhood- or adulthood-onset, duration of symptoms before baseline, FEV1 predicted, FEV1/FVC ratio, blood eosinophils, total IgE, positive or negative skin prick test, baseline asthma medication, airway hyperresponsiveness to inhaled histamine and tobacco exposure. We stratified eosinophils by: < 0.09, in-between or above 0.4.[19] Cut-offs for β_2-reversibility and peak flow variability are based on current Danish guidelines. Cut-off used for PC_{20} based on a study by Woolcock et al..[20] Annualised exacerbation rate was calculated by dividing the number of total exacerbations with years of follow-up.

We used the Cox proportional hazards model with the length of follow-up as the underlying time scale to examine the associations between characteristics obtained at baseline (1974–1990) and death. The proportional hazards assumptions were checked by testing for a non-zero slope in a generalised linear regression of the scaled Schoenfeld residuals on functions of time in continuous variables, and we checked for parallel, non-crossing Kaplan–Meier curves for categorical variables.

There were missing data on the histamine challenge test (25% missing), this was not included in the main analyses, but as a subgroup analysis including only complete cases.

Factors associated with long-term risk of exacerbations were examined by a modified cox proportional hazards model, the Prentice, Williams and Petersen gap-time model.[21] The model allowed us to account for multiple events for each participant. A gap-time model accounts for the first exacerbation affecting the likelihood of the next exacerbation. Repeated exacerbations were capped at three due to a limited number of observations with higher exacerbation frequency.

The effect of each possible factor on exacerbations and death were determined in two steps: first, in a bivariate model, adjusted for length of follow-up. The multivariable models for exacerbation and death were all adjusted for age, smoking and FEV_1% pred. The remaining variables included in the multivariable models were selected based on statistically significant association with exacerbation or death in the bivariate analyses. Statistical analyses were performed using SAS Enterprise Guide, version 7.15 (SAS Institute Inc. Cary, NC, USA). A two-tailed p-value< 0.05 was considered statistically significant.

Results

A total of 1071 persons (649 women) with asthma were included in the present analyses, and the median follow-up was 30 years (IQR 26–35 years).

Table 3 Comparison of causes of death between persons from the TRAIL cohort and the Danish background population from 1974 to 2017, stratified by age groups 0–69 and 70 +

		TRAIL (n = 357)	Denmark (n = 2 113 293)[a]	Relative Risk	95% CI
Asthma, bronchitis, emphysema and pneumonia	0–69	36 (23%)	26,811 (4%)	5.3	4.0–7.1
	70 +	57 (29%)	85,225 (6%)	5.0	4.0–6.2
Cardiovascular causes					
Ischaemic cardiovascular disease	0–69	18 (11%)	80,118 (13%)	0.89	0.6–1.4
	70 +	21 (11%)	298,467 (21%)	0.5	0.4–0.8
Other cardiac cause	0–69	5 (3%)	18,304 (3%)	1.1	0.5–2.6
	70 +	13 (7%)	95,873 (6%)	1.0	0.6–1.7
Malignancy					
Malignant neoplasm	0–69	32 (20%)	181,116 (29%)	0.7	0.5–1.0
	70 +	29 (15%)	274,408 (18%)	0.8	0.6–1.1
Airway neoplasm	0–69	5 (3%)	60,605 (10%)	0.3	0.1–0.8
	70 +	9 (5%)	69,634 (5%)	1.0	0.5–1.8
Other causes	0–69	62 (39%)	338,517 (54%)	0.7	0.6–0–9
	70 +	70 (35%)	664,233 (45%)	0.8	0.7–1.0

[a] Based on 1981–2017 data from statistics Denmark

Exacerbations

A total of 222 (20.6%) persons in the cohort had exacerbations that required hospital admission between baseline and December 31 2017; of these, 135 (13%) had one, 48 (4.5%) had two and 39 (3.6%) had three or more (up to a maximum of seven). The median time between enrolment into the cohort and first exacerbation was 18.9 (IQR 10.1–28.0 years). The median time between first and second exacerbation was 78 days (IQR 31 days to 0.5 yrs). The median time to third was 33 days (IQR 20 days to 99 days). Patients with three or more exacerbations had more tobacco exposure (50% more pack-years at baseline), almost all (85%) used SABA more than twice daily, and they had a lower level of lung function (Table 1 and Additional file 1: Table S1). Additionally, they had more pronounced airway responsiveness to histamine (lower PC_{20}), and a higher number were non-atopic.

Factors of time appeared well associated with repeated exacerbations increasing age, adult-onset asthma and duration of symptoms before baseline visit (Table 2). Poor asthma control at baseline was also associated with later exacerbations as poor FEV_1, daily symptoms, and excessive SABA usage showed higher hazard ratios. Finally, high blood eosinophils, more pronounced AHR and being non-atopic were all associated with repeated exacerbations.

Mortality

During follow-up, 357 (33%) persons died, of whom 93 died of asthma-related causes (Table 3).

All-cause mortality, after adjusting for age and year of death, was higher in the TRAIL cohort compared with the Danish background population with a standardised mortality rate (SMR) of 1.24 (95% CI 1.11–1.37, p< 0.001), which equates to an approximately 24% higher mortality rate among patients with asthma. Additional file 1: Table S2 shows mortality data stratified by age and year of death. Further analyses revealed a substantially higher proportion of deaths due to airway related causes among the TRAIL cohort than the Danish population (Table 3). Interestingly, the most pronounced difference in mortality rate was observed in the younger age groups when compared with the general Danish population. Persons aged 45 and below had an SMR of 2.47 (95% CI 1.63–3.31, p< 0.001), and those aged 46 to 69 years had an SMR of 1.56 (95% CI 1.33–1.80, p< 0.001). While those 70 years and above did not differ from the background population (SMR 0.95 95% CI 0.80–1.09, p 0.477). A comparison of baseline characteristics of persons still alive and those who died during follow-up can be seen in Table 4 for asthma-related death and all-causes in Additional file 2: Table S3. Our analyses showed that those who died of asthma-related causes were older, more often had daily respiratory symptoms and were more likely to have a negative skin prick test, i.e. being non-atopic, at baseline.

The results from the Cox proportional hazards models are presented in Table 5 and Additional file 2: Table S4 for asthma-related and all-cause mortality, respectively. Age and smoking were associated with both all-cause and asthma-related mortality. A longer time from the onset of symptoms until a person was first seen in the outpatient clinic was associated with a higher HR of asthma-related mortality. Markers of poor asthma control were also associated with long-term mortality risk. High blood eosinophils ($> 0.4 \times 10^9$/l) were associated with asthma-related mortality, but not all-cause mortality. Additionally, an interaction between asthma onset and blood eosinophils meant the risk for mortality was more pronounced for persons with childhood-onset asthma. The decade of inclusion was associated with a higher risk of all-cause mortality, in that patients with earlier inclusion into the cohort had a higher risk of early mortality. There was no association between inclusion decade and asthma-related mortality or exacerbation risk.

For all-cause mortality, an interaction between skin prick test and blood eosinophils, meaning a positive skin prick test was associated with higher all-cause mortality if blood eosinophils were $< 0.09 \times 10^9$/l.

Discussion

This was a long-term cohort follow-up of 1071 persons with a doctor's diagnosis of asthma based on objective criteria followed from baseline between 1974 and 1990 until the end of 2017 or

Table 4 Comparison of baseline characteristics of the TRAIL cohort, between those still alive and those who died of asthma-related causes

	Alive (n = 978)	Dead (n = 93)	p-value
Sex, n women (%)	599 (61)	50 (54)	0.18
Age, yrs	36 (15)	56 (12)	< 0.001
Decade of inclusion			
1974–1979	144 (15)	20 (22)	0.093
1980–1989	731 (75)	68 (73)	
1990	103 (10)	5 (5)	
Years since symptom debut	4 (2–13)	10 (3–25)	< 0.001
Ever smoker[a], n (%)	331 (33.8)	48 (52)	< 0.001
Pack-years[b]	7.7 (3.5–14)	15 (7.5–22.3)	< 0.001
History of asthma exacerbation, n (%)	159 (16)	14 (15)	0.883
Daily symptoms, n (%)	340 (35)	58 (62)	< 0.001
Daily β_2-agonist usage	2 (2–4)	4 (3–6)	< 0.001
ICS dosage at baseline	200 (0–400)	400 (0–600)	0.082
Lung function			
FEV_1% pred	85 (17.6)	62 (21.5)	0.006
FVC % pred	94 (15)	80 (19)	< 0.001
FEV_1/FVC ratio	75 (11)	61 (13)	0.024
BD Reversibility, %	18 (16–26)	28 (16–43)	< 0.001
AHR	2.35 (1.60–4.36)	2.00 (1.10–3.98)	0.280
Peak flow variability, %	22 (15–29)	23 (13–26)	0.725
Blood Eosinophils, $\times 10^9$/l	0.34 (0.21–0.57)	0.42 (0.21–0.57)	0.521
Total IgE, IU/l	125 (41–342)	105 (36–316)	0.317
Negative skin prick test, n (%)	403 (41)	66 (71)	< 0.001

Data are presented as mean (standard deviation) or median interquartile range), unless otherwise stated

AHR airway hyperresponsiveness, *BD* bronchodilator, *FEV_1* forced expiratory volume in 1 Second, *FVC* forced vital capacity, *ICS* inhaled corticosteroids, *IU* International Units

[a] Current or ex-smokers

[b] For ever smokers

death, whichever came first. Compared with the general Danish population, we found a higher mortality rate among the cohort, primarily in those of younger age. Predictors of asthma-related mortality were older age, longer symptom duration, smoking, reduced lung function, high SABA use, adult-onset disease and high blood eosinophils. Exacerbations were associated with no atopy, daily symptoms and AHR, in addition to the factors associated with mortality.

The average time between exacerbations decreased after each subsequent exacerbation. This finding correlates well with previous studies showing that recent exacerbations increase the likelihood of subsequent exacerbations.[22]

Previous exacerbations before baseline were not associated with subsequent exacerbations following baseline. The explanation is likely that previous exacerbations could be any length of time before baseline in the TRAIL study, and as shown previously, the predictive value of previous exacerbations dissipates over 5 years.[23]

The effect of increasing age seems to be the most critical predictor of repeated exacerbations across a prolonged period. This effect is not wholly understood but could partially stem from frequent viral respiratory tract infections together with decreased immune cell function. Additionally, a decreased effect of β_2-adrenergic medicine and increased non-reversible airway obstruction could play a role.[24,25]

Reduced lung function has time and again been proven to predict future exacerbations across the short term.[1] The TRAIL cohort supports the importance of low FEV_1 as a predictor and shows that its importance prevails across 30 years.

Increased inflammation and corticosteroid insensitivity short-term, followed by long-term airway remodelling, is potentially the cause of smoking's long-term predictive value of repeated exacerbations.[26]

Poor asthma control with daily symptoms or excessive use of reliever medication were of a particularly high risk of long-term exacerbations. As shown by previous studies, excessive use of SABA and poor symptom control leads to hospitalisation and, in the worst case, fatal asthma.[27,28]

To our knowledge, the finding that a negative skin prick test is predictive of repeated exacerbations has not been presented previously. Though when seen as a marker of non-atopy, it is consistent with studies showing that non-atopic asthma is harder to control and therefore have a higher likelihood of exacerbations.[29] There is a clear consensus that high eosinophil count is associated with short-term exacerbation risk, with both population and cohorts studies showing this association.[30,31] Based on our findings across 30 years, it appears that this risk continues long-term.

We found a substantially higher mortality rate among individuals

Table 5 Predictors of asthma-related mortality

	Bivariate model HR (95% CI)	Multivariable HR (95% CI)
Sex, women	1.33 (0.89–2.01)	–
Age		
15–45	1.00	1.00
46–69	16.4 (9.62–27.9)**	5.11 (2.77–9.43)**
≥ 70	29.0 (12.6–66.5)**	9.00 (3.55–22.9)**
Decade of inclusion		
1974–1979	2.25 (0.84–6.06)	–
1980–1989	1.67 (0.67–4.12)	–
1990	1.00	–
Years since symptom debut	1.05 (1.04–1.06)**	1.05 (1.03–1.07)**
Adult-onset[a]	2.63 (1.49–4.65)**	3.20 (1.42–7.21)*
Ever smoker[b]	2.07 (1.38–3.11)**	2.43 (1.58–3.74)**
Pack-years, only ever smokers	1.06 (1.04–1.08)**	1.03 (1.00–1.07)*
Previous severe exacerbation	0.58 (0.30–1.11)	–
Daily symptoms	3.21 (2.11–4.89)**	1.35 (0.86–2.12)
Daily β_2-agonist use, > 2 puffs	4.21 (2.57–6.89)**	2.11 (1.26–3.663)*
ICS prescribed at baseline, any dose	1.82 (1.17–2.84)*	1.16 (0.73–1.73)
Lung function		
FEV_1% pred. < 80%	8.28 (5.04–13.6)**	3.46 (1.94–6.16)**
FEV_1/FVC ratio, < 70%	6.58 (4.27–10.1)**	1.40 (0.84–2.33)
BD reversibility		
< 12%	1.00	–
≥ 12%	1.70 (0.88–3.29)	–
AHR, mg/ml		
< 1	0.47 (0.17–1.31)	0.95 (0.31–2.94)
≥ 1 to < 2	0.36 (0.13–0.97)*	1.03 (0.34–3.10)
≥ 2 to < 8	0.23 (0.09–0.58)*	1.61 (0.56–4.60)
≥ 8	1.00	1.00
Peak flow variability	0.84 (0.55–1.29)	–
Blood eosinophils, × 10^9/l		
< 0.09	1.78 (0.79–3.96)	1.23 (0.54–2.81)
≥ 0.09 to ≤ 0.4	1.00	1.00
> 0.4	1.56 (1.02–2.37)**	1.63 (1.05–2.53)*
Total IgE, < 150 IU/L	0.75 (0.49–1.45)	–
Negative skin prick test, n (%)	4.10 (2.62–6.44)**	0.65 (0.40–1.07)

Results from bivariate and multivariable cox proportional hazards model shown as hazard ratio (95% CI)

AHR airway hyperresponsiveness, *BD* bronchodilator, *FEV_1* forced expiratory volume in 1 second, *FVC* forced vital capacity, *IU* international units, *ICS* inhaled corticosteroids, *OCS* oral corticosteroids

[a] Age ≥ 18 years

[b] Current or ex-smokers.

*p-value < 0.05. **p-value < 0.001. Multivariable model: Wald $Chi^2 = 190$ Degrees of freedom = 13. p < 0.0001

with asthma compared with the Danish background population, which is well in line with other asthma cohort studies and epidemiological studies.[16,32] The higher mortality in the TRAIL cohort is in large part due to deaths being asthma-related (Table 1), with 26% of the fatal cases, but also higher a higher all-cause mortality rate among those aged 15–45. This is higher than other studies, Okayama et al.[12] and Lemmetyinen et al.[16] found that respiratory-related deaths accounted for 14% and 1% of deaths, respectively. This could be due to the participants in the TRAIL cohort were followed at secondary care facilities and therefore had more severe asthma than the other two cohorts, which were general population cohorts.

The drop in SMR between 1974 and 1999 and into the early 2000s match that reported by Ebmeier et al..[33] Yet, despite this drop, mortality remains higher for individuals with asthma. Suggesting that there is still room for improvement, so which factors should we consider when evaluating patients with asthma?

Of the investigated significant factors, we found excessive use of SABA, and high-blood eosinophil count was unique to asthma-related mortality, while the remaining factors were like that of all-cause mortality. Another study found a similar semblance of factors when comparing all-cause and respiratory-related mortality.[12] Potentially treatable traits associated with asthma-related mortality were excessive use of SABA, high blood eosinophils, and low FEV_1. All have been shown numerous times to affect short-term and all-cause mortality and now, based on our findings, also on long-term asthma-related mortality.[5,15]

Adult-onset and longer duration of symptoms were both associated with an increased risk of asthma-related mortality, also after adjusting for age. This finding is well in line with findings that adult-onset has a poorer prognosis and suboptimal response to treatment than childhood-onset asthma.[34] Longer disease duration has been associated with continuing inflammation and, therefore airway remodelling, which in turn leads to adverse outcomes.[35]

In the TRAIL cohort, a higher risk of all-cause mortality was associated with negative skin prick test, and this effect was more pronounced for individuals with low blood eosinophils. This finding is well in line with previous findings that individuals with non-Th2 asthma have poor outcomes.[36]

On the other end of the spectrum, individuals with a very high blood eosinophil count have a higher risk of asthma-related mortality, particularly individuals with childhood-onset asthma. This finding goes well in hand with high eosinophils predicting exacerbations as discussed above, though the association with mortality has only rarely been examined previously.[37] Furthermore, this upper limit has been shown to be associated with accelerated lung function decline previously.[38]

While inclusion spanned three decades, most patients (54%) were included between 1985 and 1990. We can, therefore, not accurately comment on whether changes in practice from the 70's to the 90's affect mortality or exacerbation, as most participants were most likely managed by similar practices.

This study's unique strength lies in the exceptionally long follow-up and reporting on asthma-related mortality. Not to be overlooked is the large number of participants who all had well-established and well-characterised asthma at baseline. In combination, this provides substantial insight into the path for adult persons followed at outpatient clinics and allows us as practitioners to provide better information at the first visit.

There are a few limitations worth mentioning. We did not gather information on prescribed medicine and symptoms after baseline, as these have most assuredly changed, we cannot account for the effects these changes might have on the disease trajectories of the participants. All participants were diagnosed with asthma based on objective criteria, and 65% were life-long

never-smokers at baseline, and we are therefore confident of this diagnosis at baseline. However, as there were no follow-up visits, we cannot account for whether any participants developed concomitant COPD during the study and can therefore not account for this factor. All participants were referred to a secondary care clinic, this may limit the generalisability.

The SMR has previously been shown to underestimate the actual mortality rate in comparison with a control group.[39] Meaning the actual mortality rate may be relatively higher than what we have reported.

Numbers of exacerbations is based on admission coding alone and not journal review. There is, therefore, a control are associated with both repeated exacerbations and asthma-related mortality. Likewise, adult-onset of asthma was associated with asthma-related mortality and longer time since disease debut was associated with both mortality and exacerbations. Finally, persons with non-atopic non-eosinophilic phenotype are at risk of all-cause mortality, while persons with very high blood eosinophils count are at particularly high risk of exacerbations and asthma-related mortality.

Abbreviations
AHR: Airway hyperresponsiveness; FEV_1: Forced expiratory volume in 1. second; FVC: Forced vital capacity; PC_{20}: The provocative concentration of histamine that results in a 20% drop in FEV_1; SABA: Short-acting β_2-agonist; SMR: Standardised mortality rate; TRAIL: Treatable traits in asthma, the impact on long-term outcome cohort.

Authors' contributions
ODT had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. ODT and CSU both contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors read and approved the finalmanuscript.

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Availability of data and materials
The data are available upon reasonable request, but analysis may require approval from the regional data safety committee for the capital region of Denmark (Videnscenter for dataanmeldelser).

Declarations
Ethics approval and consent to participate
The study was approved by the ethical committee for the Capital Region of Denmark (H-17025043), the regional data safety committee for the capital region of Denmark (P-2019-712) and The Danish Data Protection Agency (2013-41-2618). All participants signed an informed consent form.

Competing interests
Dr. Tupper reports personal fees from TEVA, outside the submitted work. Dr. Ulrik reports personal fees for lectures, advisory board meetings etc. from Sanofi, Novartis, AZ, GSK, Boehringer-Ingelheim, Chiesi, TEVA and ALK-Abello outside the submitted work.

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Antileukotrienes for the Prevention and Treatment of Chronic Lung Disease in Very Preterm Newborns: a Systematic Review

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Abstract

Background: Very preterm infants are at high risk of developing chronic lung disease, which requires respiratory support and might have long-term sequelae. As lung inflammation plays an important role in pathogenesis, antileukotrienes have been explored in both clinical and animal studies. We aimed to assess the benefits and harms of antileukotrienes for the prevention and treatment of respiratory morbidity and mortality in very preterm newborns.

Methods: In this systematic review, we included randomized trials and non-randomized studies in humans and animals reporting the effects of antileukotrienes in very preterm infants or other mammals within 10 days of birth. Our pre-specified primary outcomes were all-cause mortality and any harm, and, for the clinical studies, incidence of chronic lung disease. Included studies underwent risk of bias-assessment and data extraction performed by two authors independently. There were no language restrictions.

Results: Fifteen studies totally met our inclusion criteria: one randomized trial and four non-randomized studies in humans and 10 animal studies (five in rodents, two in lambs and one in either guinea pigs, rabbits or caprinae). All five clinical studies used montelukast and had a small sample size, ranging from 4 to 77 infants. The randomized trial (n = 60) found no difference in the incidence of chronic lung disease between the groups. Only one clinical study, which enrolled four very preterm infants and had a critical overall risk of bias, reported long-term outcomes. All other studies had unclear or greater overall risk of bias and meta-analyses were therefore deemed unfeasible. Eight of ten animal studies used leukotriene receptor antagonists as antileukotriene (montelukast in three of ten studies) and seven had an experimental study design (i.e. some animals were not exposed to antileukotrienes but no randomization). Three of the ten animal studies assessed different doses. Animal studies found no effect on the outcomes mortality, growth, or lung function related surrogate outcomes.

Conclusions: Use of antileukotrienes in very preterm infants to prevent or treat chronic lung disease is not supported by the available evidence. Large randomized trials focusing on outcomes relevant to patients, including long-term outcomes, are needed. Studies should also minimize risk of bias.

Full list of author information is available at the end of the article.

Background

Very preterm infants (born before 32 weeks' gestational age) constitute an extremely vulnerable population and are at high risk of developing chronic lung disease.[1] Chronic lung disease is a broad term, which includes bronchial asthma and bronchopulmonary dysplasia (BPD). It has been reported that BPD is the most common complication in extremely preterm infants.[2] Defining BPD remains a challenge.[3] This is mainly due to there being multiple factors involved in the underlying pathophysiology. Injury to the lungs, both before and after birth, may lead to an abnormal reparative response. This could cause flawed lung development, which can affect lung function into adult life.[2] Caffeine is the only drug that reduces the rate of BPD,[4] mortality, and neurodevelopmental disability.[5] More interventions are therefore needed to prevent and treat BPD and its consequences.

Antileukotrienes include leukotriene receptor antagonists (e.g. montelukast, zafirlukast and pranlukast) and leukotriene synthesis inhibitors (e.g. zileuton).[6] Antileukotriene receptor antagonists (LTR As) bind competitively to cysteinyl leukotriene receptors 1 and block the contractile promoting activity of leukotrienes in airway smooth muscles.

Montelukast is the most common type in clinical use, is administered once a day, and can be taken without regard to meals.[7] Zafirlukast and pranlukast are administered twice a day. The LTRA s are processed mainly in the liver,[8] metabolized mostly by CYP2C8, with the involvement of CYP2C9 CYP3A4 enzymes.[9,10] It is worth mentioning that LTRAs are substrates for transporters[11] and the s of genes In children, common montelukast induced adverse events are headaches, abdominal pain, rash, thirst, hyperkinesia, asthma and eczema.[13] Pharmacovigilance studies have also reported increased frequency sleeping disorders in infants younger than 2 years and psychiatric disorders in children aged 2 to 11 years, being more frequently reported than in adults. This led to a US FDA alert being issued for psychiatric events being associated with montelukast. Eosinophilic granulomatosis may also be associated with the use of montelukast, but the role of LTRAs in its pathogenesis is still uncertain.[15]

The drug zileuton, also an antileukotriene, has a different action mechanism from LTRAs. It works as an inhibitor of

5-lipoxygenase. The most serious concern is hepatotoxicity. Zileuton is mainly metabolized through the liver, particularly via P450 enzymes, mostly by CYP3A4.[16] This can lead to problems when using drugs such as theophylline at the same time due to impaired metabolization of theophylline. An option is to halve the dose of theophylline when starting treatment with zileuton.[8] Theophylline is an example of a methylxanthine, which are known to have a protective effect on the respiratory system.[17] Methylxanthines are natural components of cocoa-based products and beverages such as coffee, tea and yerba mate and therefore are commonly present in the human milk, thus reaching the newborn.

The properties of antileukotrienes might have the potential to be useful in the prevention and treatment of chronic lung disease in very preterm infants and they are currently used clinically based on anecdotal evidence, though not approved for this purpose. Their harms and benefits have not been assessed systematically. This systematic review aims to explore the evidence base for antileukotrienes in very preterm neonates in both clinical and animal studies.

Methods

Our methods for systematically reviewing the clinical studies are based on the template developed by the Cochrane Neonatal Review group (*Resources for Review Authors*, n.d.).[18] Two separate protocols were registered in Prospero for the clinical and animal studies, respectively,[19,20] since Prospero requires authors to register separate protocols for clinical and animal studies. An exploratory pilot search for animal studies was performed before submitting the protocols and our comprehensive search and data extraction.

Types of studies

We included randomized and non-randomized animal studies. Studies with a cross-over design were excluded due to our interest in long-term outcomes and the potential for carry-over effects.

For the clinical studies, we included randomized trials, quasi-randomized trials and non-randomized studies of intervention (NRSI). Again, we excluded trials with a cross-over design.

Types of participants

We included studies in any neonatal mammals, both term and pre term. "Neonatal" was defined as the first 10 days since birth, which is an arbitrary cut-off point that we pre-specified in our protocol. For the clinical studies, we included very preterm infants with a gestational age below 32 weeks and who were admitted to a neonatal department.

Types of interventions

For animal studies, we included studies using co-interventions and any route and dose of antileukotriene administration. We excluded studies where antileukotrienes were administered to mothers before birth or to lactating mothers. We also excluded studies where co-interventions were not available for all study arms. We included two types of studies (1) antileukotrienes versus control (either placebo, no intervention, or treatment as usual); (2) studies without any comparator (non-controlled studies).

For the clinical studies, we included two comparisons, i.e. (1) prevention and (2) treatment of chronic lung disease.

Outcomes

Animal studies

Our primary outcomes for the animal studies were: (1) survival until last follow up; (2) any harm.

Our secondary outcomes were: (1) growth; (2) lung volume to body weight ratio; (3) lung function; (4) lung histology; (5) inflammation markers for lungs: levels of interleukins (IL), i.e. IL-1β, IL-6, IL-16, IL-8/CXCL-8, IL10, IL-4, IL-13, CC Chemokines (MCP-1, 1α, 1β, 2 and 3), Krebs von den Lungen (KL-6), Clara cell secretory protein (CC16), neutrophil gelatinase-associated lipocalin (NGAL), placental growth factor, N-terminal pro-BNP (NT-pro-BNP), macrophage migration inhibitory factor, NF-κβ, Soluble ICAM, Tumor Necrosis Factor-ά, cysteinyl leukotriene (cysLT) release in bronchoalveolar lavage fluid, airway eosinophilia, mucus hyperproduction; (6) lung injury; (7) a irway hyperresponsiveness, fibrosis and smooth muscle actin expression; (8) behavioral tests; (9) markers for apoptosis; (10) pulmonary vascular resistance, Fulton index, and arterial wall structure. We included animal studies regardless of outcomes. Most of these are surrogate outcome measures, which however might provide a useful insight on pathophysiology in exploratory animal studies.

Clinical studies

Our primary outcomes for the clinical studies were: (1) all-cause mortality during initial hospitalization; (2) BPD/chronic lung disease incidence: only for comparison one (i.e. prevention of chronic lung disease) according to the three definitions:;[21-23] (3) any harm.

Secondary outcomes were: (1) all-cause neonatal (first 28 days) mortality, only for comparison one (i.e. prevention of chronic lung disease); (2) retinopathy of prematurity (any and ≥ stage 3[24]) (3) days of respiratory support; (4) days of supplemental oxygen; (5) need for mechanical ventilation (yes/no); (6) days of hospital stay; (7) major neurodevelopmental disability: cerebral palsy, developmental delay[25,26] or Griffiths Mental Development Scale[27] assessment greater than two standard deviations (SDs) below the mean), intellectual impairment (intelligence quotient (IQ) greater than two SDs below the mean), blindness (vision less than 6/60 in both eyes), or sensorineural deafness requiring amplification. We pre-planned to assess data for children aged 18 to 24 months and aged three to five years separately; (8) each component of the composite outcome "major neurodevelopmental disability"; (9) pulmonary function test at school age (as specified by study authors).

Searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library; MEDLINE via PubMed, and Embase, in September 2020. We also searched ongoing clinical trials submitted at clinicaltrials.gov and ITCRP website. We did not apply any restrictions regarding language, publication year, or publication status. Methodological filters excluding diagnostic studies were not used. Search strings for each database are listed in Appendix.

Selection of studies

Two authors independently screened titles and abstracts and retrieved the full text of potentially relevant articles. Eligibility was assessed according to our inclusion criteria. Two authors independently performed data extraction and assessed risk of bias.

Assessment of risk of bias

We used SYRCLE's risk of bias tool[28] for animal studies, which include the following seven domains: selection bias due to sequence generation, baseline characteristics or inadequate allocation concealment; performance bias due to inadequate randomization housing or blinding; detection bias due to inadequate randomization of outcome assessment or blinding; attrition bias due to incomplete outcome data; reporting bias due to selective outcome reporting; and other sources of bias.

For non-randomized clinical studies, we used the ROBINS-I[29] tool to assess the risk of bias, which include the following eight domains: bias due to confounding; bias in selection of participants into the study; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in measurement of outcomes; bias in the reported results; and the overall risk of bias. For the domain "confounding", we took into account the following confounders: antenatal steroids, gestational age, birth weight, Apgar score, indication to start antileukotrienes and level of respiratory support at study entry.

For randomized trials, we used the Cochrane Risk of Bias 2 tool,[30] which include the following five domains: bias arising from the randomization process; bias due to deviations of intended interventions; bias due to missing outcome data, bias in measurements of the outcome; bias in selection of the reported results and overall risk of bias.

Any disagreements were solved through discussion and, if necessary, by consulting a third review author.

Data analysis

We planned to use the Cochrane software RevMan 5.4[31] to synthesize and analyze data. We planned to analyze all infants and animals on an intention-to-treat basis and to use the fixed-effect model for meta-analyses because we expected a consistent treatment effect. We planned to synthesize data with risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, with 95% confidence intervals (CI). The overall certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the GRADE Handbook,[32] for our primary outcomes.

Subgroup analyses

For the animal studies, we planned the following: type of lung injury, dose and type of antileukotrienes.

For the clinical studies, we planned the following: (1) gestational age: extremely preterm infants (< 28 weeks' gestation, very preterm infants (28 to 31 + 6 weeks' gestation; (2) type of antileukotrienes: leukotriene receptor antagonists, leukotriene synthesis inhibitors; (3) age when first dose of leukotriene receptor antagonist was given; and (4) route of administration.

Results

Results of the search

Our searches for animal and clinical studies (Appendix) returned 1929 unique records. One additional study was identified through other sources (online search) while completing the review. Following screening titles and abstract, 22 studies were collected and assessed in full-text. Three animal studies were excluded because the animals were older than 10 days. Three studies were labelled as awaiting classification because the text of the conference abstracts were not available[33,34] or because a protocol registered in 2007 was apparently not followed by a publication. One ongoing uncontrolled clinical study was identified, with a planned sample size of 200 very low birth weight newborns.[35] Thus, fifteen studies were included: ten animal studies (see Table 1) and five clinical studies of which one was a randomized trial (see Table 2). Figure 1 presents the PRISMA flow chart.

Included studies

Animal studies

Of the ten included animal studies, five were in rodents (three in rats and two in mice)[36-40] and two were in lambs.[41,42] The remaining three were in either guinea pigs,[43] rabbits[44] or caprinae (sheep and goats in the same study).[45] Two studies assessed prevention of respiratory morbidity only,[36,44] while three studied treatment effects only.[37,39,40] Five studied both prevention and treatment effects.[38,41-43,45] Eight of ten studies used leukotriene receptor antagonists such as antileukotrienes (montelukast used in three studies),[36,37,39] one studied a leukotriene synthesis inhibitor[40] and one studied both types of antileukotrienes.[45] Of the 10 animal studies, seven had an experimental study design (i.e. some animals were not exposed to antileukotrienes but were not randomized) and three an observational study design (i.e. all animals were exposed to antileukotrienes). Within three of the ten studies different doses were assessed.[40,43,44]

Clinical studies

The five clinical studies included one randomized trial from Korea,[46] a non-randomized study performed in Germany and the USA,[47] and tree observational studies from Korea,[48] the UK[49] and Taiwan.[50] Four studied treatment and one studied prevention of BPD.[46] All five assessed the same leukotriene antagonist; montelukast. The administered dose of montelukast ranged from 1 to 2 mg/kg body weight. Details are provided in Table 2.

Risk of bias

Animal studies

Details of our risk of bias assessments are presented in Table 3. Overall, risk of bias was difficult to assess due to poor reporting and most domains were therefore "unclear" using the SYRCLE risk of bias tool.[28] As this tool is developed specifically for experimental animal studies, some domains were not applicable to the three non-controlled studies.[41,42,45]

The seven experimental animal studies all had unclear risk of selection bias because the randomization process and baseline characteristics were not specified. They all had an unclear risk of performance bias because none of the studies reported on random housing. The measures used to house the animals randomly within the animal room were not reported. Blinding of the investigators was also not reported. Only one study[37] was assessed as at low risk of detection bias as they reported that "all morphometric assessments were made blindly by the same observer (except for the bronchial alveolar attachments)". All studies had unclear or higher risk of reporting bias as their protocol was not available. One study reported that data for some outcomes were not shown[42] and thus had high risk of bias. The animal studies appeared free from other sources of biases.

Clinical studies

Details of our risk of bias assessments for the randomized and non-randomized studies are presented in Tables 4 and 5, respectively.

Table 1 Study characteristic animal studies

	Prevention studies (antileukotrienes are administered before inducing lung or systemic damage)		Studies on both prevention and treatment (antileukotrienes are administered before and after inducing lung or systemic damage)					Treatment studies (antileukotrienes are administered after inducing lung or systemic damage)		
	Demir 2008	**Kertesz 1992**	**Cassin 1989**	**Phillips 1995**	**Schreiber 1985**	**Schreiber 1987**	**Xiao-Yan 2020**	**Chen 2018**	**Jouvencel 2003**	**Park 2011**
Study design*	Experimental	Experimental	Observational	Experimental	Observational	Observational	Experimental	Experimental	Experimental	Experimental
Total number of animals at the very beginning	47	Not reported	24 lambs 10 goats	Not reported	6	16	72	45	24	Not reported
Number of animals which received antileukotrienes	Montelukast group n = 10 clarithromycin + montelukast + pentoxifylline combination group n = 6 (plus other study groups not relevant in this review)	Experiment 1: 31 0.1 uM/kg/h: 4 + 1 + 3 + 6 = 14 1.0 uM/kg/h: 8 + 9 = 17 experiment 2: not reported	Not reported	Prevention (normoxia): 19 (with three different doses) Treatment (hyperoxia): 22	5 (we use experiment FPL 57,231 infusion started during hypoxia, so exp 2)	5	24	Not reported	12	Not reported
Number of animals in control group	Clarithromycin n = 8 pentoxifylline n = 8 placebo n = 6	Experiment 1: 2 + 2 + 11 + 12 = 27 experiment 2: 60	No control group, i.e. all animals got antileukotrienes	Prevention (normoxia): 6 Treatment (hyperoxia): 6	No control group, i.e. all animals got antileukotrienes	No control group, i.e. all animals got antileukotrienes	24	Not reported	12	Not reported
Number of animals outcome data are reported for	47	Not reported	Sheep: 16 for antileukotrienes (plus 3 for thromboxane receptor antagonist) goats: 6 for antileukotrienes (plus 4 for thromboxane receptor antagonist)	Not reported	Not reported	Not reported	72	Not reported	16	Not reported

Table 1 (continued)

	Prevention studies (antileukotrienes are administered before inducing lung or systemic damage)		Studies on both prevention and treatment (antileukotrienes are administered before and after inducing lung or systemic damage)					Treatment studies (antileukotrienes are administered after inducing lung or systemic damage)		
	Demir 2008	**Kertesz 1992**	**Cassin 1989**	**Phillips 1995**	**Schreiber 1985**	**Schreiber 1987**	**Xiao-Yan 2020**	**Chen 2018**	**Jouvencel 2003**	**Park 2011**
Funding	Supported by Dokuz Eylul University and The Scientific and Technological Research Council of Turkey	Antileuk provided by Stuart Pharmaceuticals Study partly supported by the Dee and Moody Research Fund of Evanston Hospital	National Hear, Lung and Blood institute Grant Antileukotrienes provided by the pharma	Supported by the Medical Research Council Drug provided by Upjohn Company	Supported in part by grants from the American Lung Association and U.S.Public Health Service Program Project Grant HL 24,056	Supported in part by grants from the American Lung Association, HL35518, and US Public Health Service Program Project Grant HL24056	Funded by Jiangsu Provincial Maternal and Child Health Research Project (F201647	Funding Project of Bengbu Medical College of Science and Technology Development (No. BYKF1741)	Grant sponsor: Société Française de Médecine Néonatale; Montelukast sodium a gift from Merck, Sharp and Dohme, Whitehouse Station, NJ	Medical Grant Program of Merck Sharp and Dohme Corp. (Rahway, NJ, USA), who also supplied with MK-0591 in powder form
Species	Rats	Rabbits	Sheep, goats	Guinea pig	Lambs	Lambs	Rats	Mice	Rats	Mice
Strain	Wistar	New Zealand albino	Not reported	Not reported	Mixed-breed	Not reported	Clean level P3 SD	57BL/6 J	Wistar	FVB/n
Age when antileuk/comparator were given	Postnatal days 3–13	day 7	Five days. Unclear, but it is likely that the animals were given antileukotrienes and were exposed to hypoxia at the same day	day 3–6	day 3–7	day 4–6	Not reported	day 2–14	day 4	Treatment windows were from days 1–4, 5–9 or 10–14 after birth
Presence and degree of prematurity	Full term	Full term	Not reported	Pre-term	Not reported	Not reported	Likely Full term	Likely Full term	Likely Full term	Full term
Mode of delivery	Naturally delivered	Not reported	Not reported	Caesarean section	Not reported	Not reported	Not reported	Not reported	Not reported	Naturally delivered
Type of lung damage/insult	Hyperoxia	Hyperoxia > 95% O_2	Hypoxia, ventilation	Hyperoxia 95%O_2	Hypoxia	LTD4 injection	Hypoxia	Hyperoxia	Hyperoxia 50% O_2 from P0 to P15	Hyperoxia 85% O_2

Table 1 (continued)

	Prevention studies (antileukotrienes are administered before inducing lung or systemic damage)		Studies on both prevention and treatment (antileukotrienes are administered before and after inducing lung or systemic damage)					Treatment studies (antileukotrienes are administered after inducing lung or systemic damage)		
	Demir 2008	**Kertesz 1992**	**Cassin 1989**	**Phillips 1995**	**Schreiber 1985**	**Schreiber 1987**	**Xiao-Yan 2020**	**Chen 2018**	**Jouvencel 2003**	**Park 2011**
Age at lung damage	Days 3–13	Day 7	Five days. Unclear, but it is likely that the animals were given antileukotrienes and were exposed to hypoxia at the same day	days 1–3	Days 3–7	Days 4–6	Not reported	12 h, hyperoxia for 7 consecutive days	Within 24 h of birth	Within 24 h of birth
Type of control group	Clarithromycin Pentoxifylline Placebo	Vehicle	No control group, i.e. all animals got antileukotrienes	Vehicle	No control group, i.e. all animals got antileukotrienes	No control group, i.e. all animals got antileukotrienes	Saline for periventricular leukomalacia group	Saline (0.9% NaCl)	Saline	Vehicle (5% ethanol; 1% Tween 80)
Name of antileuk/name of comparator	Antileuk: Montelukast, Montelukast + pentoxifylline + clarithromycin combination Comparator: clarithromycin pentoxifylline	INTERVENTION ICI 198,615 (leukotriene receptor antagonist) CONTROL vehicle consisting of polyethylene glycol 400 (PEG 4OO), 1 M NaOH, and phosphate buffered saline (PBS)	Leukotriene receptor antagonist L 649923 Dual cyclooxygenease and lipoxygenase inhibitor BW 755C	U-75302 (LTB4 antagonist)	FPL57231 (leukotriene receptor antagonist)	FPL57231 (leukotriene receptor antagonist)	INTERVENTION Pranlukast CONTROL Saline	Antileuk: montelukast sodium Control: Saline	INTERVENTION Montelukast sodium CONTROL Normal saline	INTERVENTION MK-0591 (5-lipoxygenase-activating protein inhibitor) CONTROL vehicle

Table 1 (continued)

	Prevention studies (antileukotrienes are administered before inducing lung or systemic damage)		Studies on both prevention and treatment (antileukotrienes are administered before and after inducing lung or systemic damage)					Treatment studies (antileukotrienes are administered after inducing lung or systemic damage)		
	Demir 2008	**Kertesz 1992**	**Cassin 1989**	**Phillips 1995**	**Schreiber 1985**	**Schreiber 1987**	**Xiao-Yan 2020**	**Chen 2018**	**Jouvencel 2003**	**Park 2011**
Dose	INTERVENTION montelukast: 1 mg/kg/day one dose combination: clarithromycin 100 mg/kg in two doses per day, montelukast 1 mg/kg/day, pentoxifylline 150 mg/kg in two doses per day CONTROL clarithromycin: 100 mg/kg/day in two doses pentoxifylline: 150 mg/kg/day in two doses saline: not reported	INTERVENTION experiment 1: two groups group 1: 0.1 uM/kg/h ICI group 2: 1.0 uM/kg/h ICI Experiment 2: 0.1 uM/kg/h CONTROL not reported	L 649,923: prepared in saline daily (10 mg/ml) and injected (5,86 mg/kg) over a 2 min period BW 755C: prepared in saline (8,8 mg/ml) and administered (30 mg/kg) over a 2- to 5-min period	3.0 mg/100 g body wt**	2 mg/kg/min (total 20 mg/kg)	2 mg/kg/min (total 20 mg/kg)	0.1 mg/kg	Montelukast 10 mg/kg Saline not reported	INTERVENTION 1 mg/kg/day (diluted in normal saline to 200mcg/ml—injected 5 mcg/g) CONTROL 5 mcg/g	INTERVENTION 40 mg/kg **

Table 1 (continued)

	Prevention studies (antileukotrienes are administered before inducing lung or systemic damage)		Studies on both prevention and treatment (antileukotrienes are administered before and after inducing lung or systemic damage)					Treatment studies (antileukotrienes are administered after inducing lung or systemic damage)		
	Demir 2008	**Kertesz 1992**	**Cassin 1989**	**Phillips 1995**	**Schreiber 1985**	**Schreiber 1987**	**Xiao-Yan 2020**	**Chen 2018**	**Jouvencel 2003**	**Park 2011**
Frequency	INTERVENTION montelukast: 1 dose per day combination: clarithromycin in two doses per day, montelukast 1 dose per day, pentoxifylline in two doses per day CONTROL clarithromycin: in two doses per day pentoxifylline: in two doses per day saline: once daily	Continuous by micropump pumping 0.5 uL/h	We suspect that the drugs were only given once, but this cannot be extracted from the text with complete certainty	Every 12 h over a 72 h period	Once for 10 min	Once for 10 min	once every 12 h, for 3 consecutive days	Once every other day	1/day, from days 4–14	Once daily during the treatment window
Route of administration	INTERVENTION subcutaneously CONTROL clarithromycin: subcutaneously pentoxifylline: injected intraperitoneally saline: not reported	Subcutaneous pump	L 649,923: injected directly into the pulmonary circulation BW 755C: administered via femoral artery	Not reported	Infusion	Intravenous infusion	Intraperitoneal injection	Intraperitoneally	Subcutaneously	Subcutaneously

* Experimental: Compares outcomes with vs without antileuk administration (not all animals received antileuk); Observational: Compares outcomes before vs after antileuk administration (all animals received antileuk)

** The study reports results for different doses

None of the included studies reported on the following characteristics: protocol registration, immune status, sex, initiation dose

Table 2 Study characteristics clinical studies

	Cheng 2014	Kim 2015	Min Kim 2009	Panjwani 2016	Rupprecht 2014
Country	Taiwan	Korea	Korea	UK	Germany, USA
Protocol registration	Not reported	NCT01717625	Not reported	Not reported	DRKS00004763
Study design	Retrospective cohort	Multicenter, prospective, randomized, open labelled, parallel group, intervention trial	cohort study (preliminary investigation with the historical control group)	cohort study (all infants received antileukotrienes)	Unblinded, prospective trial (not-randomized)
Duration of follow-up	Unclear. At least two years based on info from Table 3 (MDI and PDI)	36 weeks GA, or the discharge date	12 weeks	Not reported	Treatment was continued until the radiological signs and the clinical symptoms of BPD disappeared or discharge
Completeness of follow-up	4/4	Intervention group: 30/37 Control group 36/40	15/15	13/13	intervention group: 10/11 (1 died) Control group: 4/11 (7 died)
Funding	Not reported	This study was supported by the research fund of the Korea Food and Drug Administration (KFDA)	Not reported	Not reported	Partly funded by an unrestricted grant from the Oberfrankenstiftung, Bayreuth, Germany, which had no influence on the design, collection, analysis, or interpretation of data or publication
Mode of delivery	Not reported	Not reported	INTERVENTION VD 4, C-Sect. 11 CONTROL VD 3, C-Sect. 12	Not reported	Not reported
Type of control group	No control group	Unclear	Standard treatment of BPD in the historical control group	No control group	Conventional therapy regimen
Total number of infants in intervention/control group	4	INTERVENTION 37 CONTROL 40	INTERVENTION 15 CONTROL 15	13	INTERVENTION 11 CONTROL 11
Gestational age	Ranging 24–30	INTERVENTION Mean 27.6 SD 1.6 CONTROL Mean 27.3 SD 1.6	INTERVENTION mean 27.3 SD 2.2 WEEKS CONTROL mean 27.1 SD 2.1 WEEKS	Mean gestation 25 + 3 weeks	INTERVENTION Mean 25.3 SD 1.6 CONTROL Mean 25.6 SD 1.3
Birth weight	Ranging 605–1490 g	INTERVENTION: 1,097 SD 327 CONTROL: 997 SD 235	INTERVENTION mean 913.7 SD 206.4 CONTROL mean 982.7 SD 260.1	Mean birth weight 746 g	INTERVENTION Mean 658 SD 138 CONTROL Mean 624 SD 144
Sex	Not reported	Not reported	INTERVENTION male 7, female 8 CONTROL male 7, female 8	Not reported	INTERVENTION male 7, female 4 CONTROL male, 7, female 4

Table 2 (continued)

	Cheng 2014	Kim 2015	Min Kim 2009	Panjwani 2016	Rupprecht 2014
Criteria (if any) to give intervention	Montelukast was given as rescue therapy when the patients' chest X-rays showed fibrosis or increased infiltration; or when the patient required higher or prolonged ventilator support, which was defined as FiO2 ≥ 30%, PIP ≥ 20 cm H2O and ventilator usage more than nine days	< 32 weeks, > 14 days old on O2 or mechanical ventilation; > 20 cal/kg/day by enteral feeding	Existing BPD, admitted to the NICU except for cases where oxygen dependence other than lung diseases such as congenital anomalies, heart disease, and brain lesions may occur	"Last resort" in infants with significant oxygen requirement and radiological changes of significant lung disease unresponsive to postnatal steroids	Preterm infants with life-threatening BPD were chosen as the study group, with a probability of survival rated equal to or less than 50% by the attending physician. Further inclusion criteria for this study were a gestational age of less than 32 weeks, a birth weight of less than 1,500 g, and the need for mechanical ventilation support at day 28 after birth
Age when antileuk/comparator is given,	Not reported. Infants seem to be a few weeks old because of the reported body weight when the intervention was administered	INTERVENTION 31.3 SD 1.3 CONTROL 30.6 SD 1.6	Unclear	Not reported	Not clear. The recommended initiation of therapy was defined as the period between days 28 and 45 of life and as early as possible
Name of antileukotriene/comparator	Montelukast	Montelukast	Montelukast Sodium	Montelukast	Montelukast
Formulation	Singulair	Singulair	Singulair	Not reported	Not reported
Initiation	Not reported	Not reported	Not reported		1 mg/kg of body weight in the 1st week of therapy
Dose	2 mg	According to body weight (less than 1,000 g, 0.5 mg; 1,000 g to 1,500 g, 1.0 mg; 1,500 g to 2,000 g, 1.5 mg; greater than 2,000 g, 2 mg)	1 mg/kg	"2 mg/kg or 2 mg" (unclear reporting)	1 mg/kg of body weight in the 1st week of therapy, increasing to 1.5 mg/ kg of body weight in the 2nd week and finally to 2 mg/kg of body weight in the 3rd week
Frequency	Once daily for at least 28 days	Once daily until 36 weeks GA or until discharge	Twice a day for the average of 12 weeks	once daily	single dose, daily
Route of administration	Not reported	Orogastric tube or by oral administration	Orally	Orally	Not reported
Co-interventions	Not reported	Surfactant	Standard treatment for BPD	Not reported	All infants had varying concomitant medications administered (e.g. methylxanthines, steroids, and diuretics)

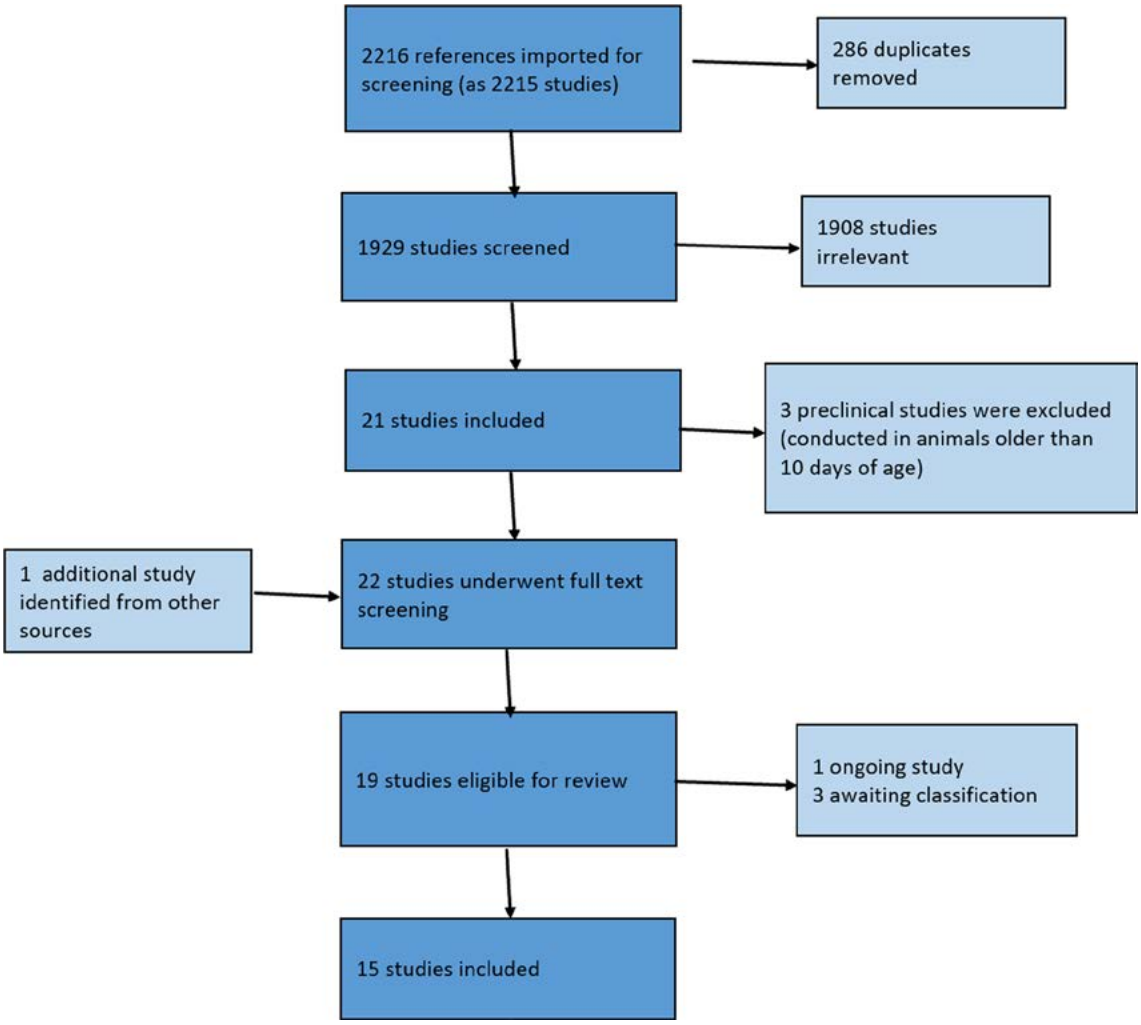

Fig. 1 PRISMA flow diagram

None of the included clinical studies were assessed to have low risk of bias. The single included RCT had an overall risk of bias assessed as "some concerns"[46] due to missing information about the randomization process; unclear description of the infants that were not included in the final analysis and because it was unclear whether the outcome assessors were blinded. The cohort study did not clearly define inclusion and exclusion criteria and was therefore assessed to have serious risk of bias.[48] The study by Rupprecht et al.[47] was scored with an overall critical risk of bias because of confounding as the control group consisted of children whose parents provided informed consent for participation as a control group patient but not for administration of the medication montelukast. The reasons for only allowing the child into the control group are not reported. This leads to critical risk of bias in the domain 'bias due to confounding'. The infants in the control group could have been potentially sicker than those in the montelukast group, in which case the parents might not be willing to try a drug with unknown effects on their fragile child. Therefore, the reduced rate of mortality in the infants treated with montelukast could be markedly different from the true effect. The study by Panjwani et al.[49] had a serious risk of bias. The study used a historical cohort as comparator and there was no clear definition of their inclusion and exclusion criteria. The study by Cheng et al.[50] had an overall critical risk of bias as a historical cohort design was used without clear inclusion and exclusion criteria.

Effects of the interventions

Meta-analysis of the clinical and the animal studies was not deemed feasible for any of the outcomes since they were reported by too few studies with highly variable designs and were assessed with outcome measures which could not be meaningfully pooled.

Animal studies

Table 6 shows the list of the outcomes reported by each study. Four controlled studies reported on mortality and found no significant effect;[36,37,40,44] two controlled studies reported on growth;[36,37] no significant effect was found in either study between combination treatment (montelukast, clarithromycin and pentoxifylline combination) versus placebo.

We made the post hoc decision to include the reported outcome 'lung weight to body weight ratio', in addition to our prespecified outcome lung volume to body weight. No statistically significant difference was found in the three studies reporting on either of the two outcomes.[37,39,44]

Five experimental studies assessed lung histology, reporting on different outcomes, i.e. radial alveolar count,[39] alveolar surface area,[36] parenchymal tissue,[37] number of airspaces[40] and percentage of airspace.[43] No firm conclusions could be drawn (see Table 6 for more information).

Table 3 SYRCLE risk of bias table

Study ID	Cassin 1989	Chen 2018	Demir 2008	Jouvencel 2003	Kertesz 1992	Park 2011	Phillips 1995	Schreiber 1985	Schreiber 1987	Xiao-Yan 2020
1. Selection bias- Sequence generation	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported
2. Selection bias- Baseline characteristics	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported
3. Selection bias- Allocation concealment	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported
4. Performance bias- Random housing	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported	Unclear risk The different groups were at least raised in the same room, but this does not report enough about the random housing	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported
5. Performance bias- Blinding	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported
6. Detection bias- Random outcome assessment	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Random outcome assessment for one outcome; unclear for others	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported

Table 3 (continued)

Study ID	Cassin 1989	Chen 2018	Demir 2008	Jouvencel 2003	Kertesz 1992	Park 2011	Phillips 1995	Schreiber 1985	Schreiber 1987	Xiao-Yan 2020
7. Detection bias- Blinding	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported	Unclear risk Tissues were prepared in a blinded fashion, although there is no information about blinding all the outcome assessors	Low risk Quote: "All morphometric assessments were made blindly by the same observer (P.J.) (except for the bronchial alveolar attachments, by M.F.) on images of all lung sections"	Unclear risk Not reported	Unclear risk Not reported	Unclear risk Not reported	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Not applicable There is no control group, i.e. all the animals got antileukotrienes	Unclear risk Not reported
8. Attrition bias- Incomplete outcome data	Unclear risk Unclear if outcome data are reported for all animals	Unclear risk Unclear if outcome data are reported for all animals	Low risk All animals were included in the analysis	Unclear risk Unclear if outcome data are reported for all animals	Unclear risk Unclear if outcome data are reported for all animals	Unclear risk Unclear if outcome data are reported for all animals	Unclear risk Unclear if outcome data are reported for all animals	Unclear risk Unclear if outcome data are reported for all animals	Unclear risk Unclear if outcome data are reported for all animals	High risk Quote "any loss of sample size due to deaths was made up for by random sampling"
9. Reporting bias- Selective outcome reporting	Unclear risk Protocol not available	Unclear risk Protocol not available	Unclear risk Protocol not available	Unclear risk Protocol not available	Unclear risk Protocol not available	Unclear risk Protocol not available	Unclear risk Protocol not available	Unclear risk Protocol not available	High risk Protocol not available; moreover, the study authors report that data for some outcomes are not shown	Unclear risk Protocol not available
10. Other- Other sources of bias	Low risk None relevant	Low risk None relevant	Low risk None relevant	Low risk None relevant	Low risk None relevant	Low risk None relevant	Low risk None relevant	Low risk None relevant	Low risk None relevant	Low risk None relevant

Legend of the colours in the table: green = low risk of bias, orange = unclear, red = high; grey = not applicable

Table 4 Risk of Bias assessment with Rob 2.0 tool for the included RCT

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall risk of bias
Kim 2015	some concerns[a]	some concerns[b]	low[c]	some concerns[d]	low[e]	some concerns

[a] No information about allocation concealment, randomization of groups was performed using shuffled blocks of random numbers in Microsoft Office, Excel 2007

[b] Unclear description of the infants that were not included in the final analysis

[c] Data appears to be complete. Attrition and exclusions were explained (not completely clear though) and accounted for

[d] Unclear if outcome assessors were blinded

[e] Seems in accordance with protocol

Table 5 Risk of Bias assessment with ROBINS-I tool for the included non-randomized studies

	Confounding	Selection of participants into the study	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported results	Overall risk of bias
Rupprecht 2014	Critical[a]	Low	Low	Low	Low	Moderate[f]	Low	Critical
Min Kim 2009	Low[b]	Serious[c]	Low	Moderate[d]	Moderate[e]	Moderate[g]	Moderate[h]	Serious
Panjwani 2016	No information	Serious[i]	No information	No information	No information	No information	No information [j]	Serious
Cheng 2014	No information[k]	Critical [l]	Moderate[m]	Low	No information	Moderate[n]	Moderate[o]	Critical

[a] The control group consisted of children whose parents provided informed consent for participation in this study (as a control group patient) but not for administration of the medication montelukast (controls 1–5, 8,and 9; Table 1); and children in whom the planned therapy scheme was not possible due to existing or arising contraindications for the study drug (4 children, phenobarbital therapy in controls 6, 7, 10, and 11)

[b] No significant difference between groups regarding patients' characteristics

[c] There is no clear definition of inclusion and exclusion criteria

[d] The study does not specify the exact time for which montelukast was given and for how long co-interventions of the conservative treatment were given, which may lead to relevant differences in co-interventions

[e] Data appears to be complete, although no protocol was published and the study was not registered as a clinical study

[f] Outcome "Duration for mechanical ventilation" might be biased by unblinded outcome assessor

[g] Outcome "Need for mechanical ventilation" might be biased by unblinded outcome assessor

[h] There is a discrepancy between text of the results section and table about vomiting or diarrhea as an adverse effect

[i] The study uses historical cohort as comparator, there is no clear definition of inclusion criteria, exclusion criteria are not well-specified

[j] Only abstract is available

[k] Information about possible confounding is insufficient

[l] Historical cohort, no clear definition of inclusion and exclusion criteria, no control group

[m] Subjective inclusion criteria

[n] Outcomes 'hospital stay' and 'respiratory support (duration, days)' are subjective

[o] No protocol published

Three studies reported on inflammation markers for lungs.[39,43,44] Two studies[43,44] reported on polymorphonuclear leukocytes and protein in bronchoalveolar fluid. Phillips et al.[43] showed a reduction in the number of neutrophils and protein in the treated hypoxia group and in eosinophils in the treated normoxia group. The study by Chen et al.[39] detected a reduction in the concentration of other inflammation markers in the lung tissue of BPD mice.

Lung injury was reported in one study in which montelukast treatment decreased malondialdehyde levels and enhanced superoxide dismutase activity in the lung tissues of the BPD mice.[39]

The study by Demir et al.[36] was the only study to report fibrosis and smooth muscle actin expression. They did not detect an effect of montelukast alone versus placebo; the combination treatment (montelukast, clarithromycin and pentoxifylline combination) did result in a lower actin score compared to the placebo group.

Only one study reported on behavioral tests, the Morris water maze experiment.[38] There was an improvement in escape latency in the pranlukast group and the number of times rats in the pranlukast group crossed the platform in the maze increased.

The study by Schreiber et al.[41] found a decrease in pulmonary vascular resistance in lambs after antileukotriene infusion.

None of the animal studies reported on harms, lung function, markers for apoptosis, Fulton index or arterial wall structure.

Table 6 Outcomes antileukotrienes animals

	Chen 2018	Demir 2008	Jouvencel 2003	Kertesz 1992	Park 2011	Phillips 1995	Schreiber 1985	Xiao-Yan 2020
Mortality	Not reported	See note 1	See note 2	See note 3	See note 4	See note 5	Not reported	See note 6
Somatic growth	Not reported	See note 7	See note 8	Not reported	Not reported	Not reported	Not reported	Not reported
Lung volume to body weight	See note 9	Not reported	See note 10	See note 11	Not reported	Not reported	Not reported	Not reported
Lung histology	See note 12	See note 13	See note 14	Not reported	See note 15	See note 16	Not reported	Not reported
Inflammation markers for lungs	See note 17	Not reported	Not reported	See note 18	Not reported	See note 19	Not reported	Not reported
Lung injury	See note 20	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Airway hyperresponsiveness, fibrosis and smooth muscle actin expression	Not reported	See note 21	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Behavioral tests	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	See note 22
Pulmonary vascular resistance	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	See note 23	Not reported

None of the included studies reported on the following outcomes: Harms, lung function, markers for apoptosis, Fulton index, arterial wall structure

Schreiber 1987 and Cassin 1989 are not listed in the table as they reported none of the outcomes specified in our review

Intervention: montelukast 0/10 combination: 0/6 Control: clarithromycin 0/8 pentoxifylline 0/8 placebo 0/6

Intervention 0/12. Control 0/12

Experiment 1: not reported Experiment 2: intervention: the percent mortality of the rabbits at any given number of hours of exposure to > 95% (%) (48 h: 0; 60 h: 43; 84 h: 65 108 h: 88 132 h: 88). Control: experiment 2: The percent mortality of the rabbits at any given number of hours of exposure to > 95% (%) (48 h: 0; 60 h: 41; 84 h: 59 108 h: 79 132 h: 100). There were no significant differences at any time between the ICI and the control group

There was no mortality among study animals

In the prevention study (normoxia), 3 out of 19 and 1 out of 6 pups died in the antileukotriene and control group, respectively. In the treatment study (hyperoxia), 3 out of 22 and 0 out of 6 pups died in the antileukotriene and control group, respectively

This outcome cannot be calculated because "any loss of sample size due to deaths was made up for by random sampling

Intervention: montelukast: Me 13 SD 0.6 g; combination: Me 10.1 SD 1.1 g;;control clarithromycin: Me 9.3 SD 0.7 g; pentoxifylline: Me 9.2 SD 3.2; placebo: Me 11.6 SD 2.2 g; montelukast vs placebo $p = 0.07$; montelukast vs. clarithromycin $p < 0.0001$; montelukast vs. pentoxifylline $p = 0.0019$; combination vs. placebo $p = 0.1661$

Intervention: mean 28.8 SD 0.5(g) (not relevant); control: Mean 28.5 SD 0.4 g (not relevant)

LW/BW intervention: Not reported, → lung weight/body weight (LW/BW): It is impossible to extract the data due to wrong values on y-axis)

Intervention: Mean 5.3 SD 0.13(ml/100 g) (not relevant) control: Mean 5.15 SD 0.13 (not relevant)

LW/BW intervention: not reported(Lung water expressed as lung wet weight to body weight ratios 0.1 μM/kg/h ICI 48 h: 1.3 SD ?; 72 h: 5,7 SD 0.2; 84 h: 7.6 SD 0,4 96 h: 7.5 SD 0.5; 1.0 μM/kg/h ICI 84 h: 7.5 SD ?; 96 h: 6,6 SD 0.3). Control: lung wet weight: body weight ratios began to increase at 72 h and continued to increase slowly after 84 and 96 h of hyperoxic exposure. No differences between intervention and control group (Fig. 3b) Control Lung water expressed as lung wet weight to body weight ratios control 48 h: 1.7 SD ?; 72 h: 5.4 SD 0.2; 84 h: 6.2 SD 0.4 96 h: 6.3 SD 0.5

Intervention: mean linear intercept (MLI): 93 SD .5; radial alveolar count (RAC) mean: 4.28 SD 0.24—both $p < 0.01$ vs hyperoxia model. Control: mean linear intercept (MLI): 130 SD 7.7; radial alveolar count (RAC): 1.94 SD 0.1

Intervention: alveolar surface area (%): group 3 montelukast Me 41.6 SD 4.8; group 5 combination: Me 64.0 SD 3; control: alveolar surface area (%); clarithromycin Me 50.9 SD 4.2; pentoxifylline Me 59.4 SD 6.8; placebo Me 50.2 SD 10.4. montelukast vs. placebo $p = 0.0389$ montelukast vs. clarithromycin $p = 0.0005$ montelukast vs. pentoxifylline $p < 0.0001$ combination vs. placebo $p = 0.0093$

Intervention: surface density of parenchymal tissue mean 24.2 SD 1.2 (%) (not relevant); mean linear chord length mean 53.3 SD 1.3 (μm) (not relevant) septal attachments (/mm bronchi) mean 29.1 SD 1.0 (not relevant). Control: surface density of parenchymal tissue mean 22.8 SD 0.5 (not relevant); mean linear chord length mean 52.7 SD 1.3(not relevant) septal attachments (/mm bronchi) mean31.7 SD 0.9 (not relevant)

Number of airspaces intervention: treatment group: (dose 40 mg/kg, P10-14): mean 20 SD 2. Prevention group (dose 40 mg/kg, p1–4): mean 19 SD 1 control treatment group (dose 0 mg/kg, P10–14): mean 11 SD ? prevention: (dose 0 mg/kg, p1–4): mean 6 SD 2

95% oxygen + treatment: airspace (%) (37.0 SD 6.0) neutrophils (No mm^{-2}) (198 SD 10.9 (Different from 95% O, control, $p < 0.05$)) lung sections from pre-term guinea pig pups. 21% oxygen + treatment: airspace (%) (43.5 SD 3.5) neutrophils (No mm^2) (108 SD 8.5) lung sections from pre-term guinea pig pup

Intervention: relative TNF-α mRNA level mean: 2.0 SD 0.15; relative IL-6 mRNA level mean: 1.7 SD 0.06; relative IL-1β mRNA level: 1.9 SD 0.12; [not sure about p value, in the text: "Montelukast treatment significantly reduced the levels of TNF-a, IL-6, and IL-1b in the lung tissues of the BPD mice. control: relative TNF-α mRNA level mean: 3.3 SD 0.1; relative IL-6 mRNA level mean: 3.5 SD 0.2; relative IL-1β mRNA level mean: 2.9 SD 0.1

Intervention: Dose 0.1 μM/kg/h: Total protein recovered from BAL mean (μg/ml) (48 h and 72 h: 90 SD 20; 84 h: 250 SD 120; 96 h: 330 SD 40); PMNS represented as a percentage of the total (48 h: 0; 72 h: 1,3 SE 7; 84 h: 10 SE 5; 96 h: 18 SE 5) white cells recovered from BAL mean (%); PMNs, represented as the absolute number recovered from BAL of the left lung (× 100,000) (48 h and 72 h: 0.5 SE 0.2; 84 h: 2,4 SE 0.3 96 h: 2.9 SE 0.3); 6-Keto-PGF 1 alfa the stable metabolite of PGI, in pg/ml (48 h: 71 SE no info; 72 h: 54 SE 28; 84 h: 144 SE 50; 96 h: 347 SE 463); TXB, the stable metabolite of TXA, in pg/ml mean (48 h: 115 SE no info; 72 h: 81 SE 19; 84 h: 241 SE 121; 96 h: 207 SE 22). Dose 1.0 uM/kg/h: total protein recovered from BAL mean (μg/ml) (84 h: 475 SD 112; 96 h: 416 SD 56); PMNS represented as a percentage of the total (48 h: 0; 72 h: no info; 84 h: 20 SE 4; 96 h: 14 SE 5) white cells recovered from BAL mean (%); PMNs, represented as the absolute number recovered from BAL of the left lung (× 100,000) (48 h and 72 h: no info; 84 h: 2,9 SE 0.3 96 h: 2.1 SE 0.); 6-Keto-PGF, the stable metabolite of PGI, in pg/ml (48 h: no info; 72 h: no info; 84 h: 348 SE 32;

Clinical studies

Outcomes for the randomized trial[46] and the four non-randomized[47-50] clinical studies are reported in Table 7.

Two clinical studies reported on all-cause mortality;[47,48] only one study,[47] non-randomized, reported on all-cause mortality for both the intervention and the control group and found a significant reduction in all-cause mortality in the montelukast group.

The two studies that reported on frequency and the severity classification of BPD showed no relevant difference between case and control group.[46,48]

Table 6 (continued)

96 h: 315 SE 32); TXB, the stable metabolite of TXA, in pg/ml mean (48 h: no info; 72 h: no info; 84 h: 211 SE 19; 96 h: 259 SE 37)

Control: total protein recovered from BAL mean (µg/ml) (48 h and 72 h: 90 SD 20; 84 h: 392 SD 61; 96 h: 420 SD 56) PMNS represented as a percentage of the total (48 h: 0; 72 h: 1,3 SE 8; 84 h: 22 SE 5; 96 h: 21 SE 4) white cells recovered from BAL mean (%); PMNs, represented as the absolute number recovered from BAL of the left lung (× 100 000) (48 h and 72 h: 0.5 SE 0.2; 84 h: 3,4 SE 0,3 96 h: 3,5 SE 0,2); 6-Keto-PGF, the stable metabolite of PGI, in (48 h: 71 SE no info; 72 h: 54 SE 28; 84 h: 222 SE 32; 96 h: 265 SE 44) TXB, the stable metabolite of TXA, in pg/ml mean (48 h: 115 SE no info; 72 h: 81 SE 19; 84 h: 241 SE 121; 96 h: 207 SE 22) pg/ml

95% oxygen + treatment: neutrophil and eosinophil numbers and protein concentration in bronchoalveolar lavage fluid (BALF) neutrophils (10 4 ml-' BALF) 3.0: 1.85 SD 0.79 (Different from equivalent vehicle control, PcO.05.)) eosinophils (10 6 ml -' BALF) 3,0: 0.88 SD 0.37 protein (mg ml -' BALF) 3,0: 0.28 SD 0.127). 21% oxygen + treatment: neutrophil and eosinophil numbers and protein concentration in bronchoalveolar lavage fluid (BALF) neutrophils(10 4 ml-' BALF) 3,0: 1.45 SD 1.56 eosinophils (10 6 ml -' BALF) 3.0: 0.94 SD 0.31(Different from equivalent vehicle control, PcO.05.) protein (mg ml -' BALF)3.0: 0.27 SD 0.08)

Intervention: oxidative stress malondialdehyde 1.4 +—0.1 mcmol/g (mean, sd); SOD superoxide dismutase 22.0 +—1 IU/mg (mean, sd). Control: oxidative stress malondialdehyde 1.9 +—0.05 mcmol/g (mean, sd); SOD superoxide dismutase 16.5 + 1 IU/mg (mean, sd)

Degree of fibrosis absent /mild /moderate /marked Intervention: group 3 montelukast 0/1/6/3 group 5 combination: 4/2/0/0. Control: clarithromycin 0/1/3/4 pentoxifylline 2/2/4/0 placebo0/2/3/1. Actin score (density x intensity) Intervention: group 3 montelukast: 5 (2–9) group 5 combination: 0 (0–1) Control: clarithromycin 7.5 (2–9) pentoxifylline 1.5 (0–6) placebo 7 (2–12)

Compared with the PVL group, the escape latency of the rats in the Pran group was shortened ($p < 0.05$) (Table 2). On the 5th day of the experiment, there was a statistically significant difference in the number of times the rats in each group crossed the platform ($F = 12.59$, $p < 0.001$). Compared with the PVL group, the number of times (1.86 ± 0.23) of rats in the Pran group crossed the platform increased ($p < 0.05$)

Intervention: me 44.0 SD 7.0 in mmHg 1-1 min^{-1} kg^{-1}. Control: me 70.3 SD 15.5 ($p < 0.05$ vs hypoxia + FPL 57,231) in mmHg1-1 min^{-1} kg^{-1} $p = 0.0086$

The occurrence of adverse events did not differ between intervention and control groups in either the randomized trial[46] or the observational study by Kim.[48] It was unclear whether the other three studies had planned to report adverse events, but they did not.

Rupprecht et al.[47] did not provide information about the timing of drug administration and therefore all-cause neonatal mortality could not be extracted from the study for our pre-defined time point. Kim et al.,[46] Panjwani et al.[49] and Min Kim et al.[48] did not report all-cause neonatal mortality.

Rupprecht et al.[47] reported a significantly shorter duration of respiratory support in the group receiving montelukast compared to controls (41.2 ± 25.3 vs. 103.7 ± 90.6 days).

Two studies reported on mechanical ventilation and found no differences.[46,48]

None of the included studies reported on fraction of inspired oxygen duration or pulmonary function testing at school age.

GRADE assessment

The certainty of the evidence was "very low" for all outcomes because of imprecision and high risk of bias in multiple other domains, both in clinical and animal studies.

Discussion

Summary of main findings

In this systematic review, we aimed to systematically assess the effects of antileukotrienes for the prevention and treatment of chronic lung disease in very preterm newborns. We included five clinical studies and ten animal studies. The clinical studies consisted of one RCT and four non-randomized studies. These five clinical studies and three of the animal studies examined the leukotriene antagonist montelukast. We did not find it meaningful to pool results because of the differences in study design and the high overall risk of bias. Drawing definitive conclusions on basis of the existing evidence is thus not possible.

Overall completeness and applicability of evidence

The animal studies had an overall unclear risk of bias due to poor reporting. None of the experimental studies reported on sequence generation, baseline characteristics, allocation concealment, random housing, blinding of the caregivers or random outcome assessment. Only Jouvencel[37] reported adequately on blinding of the outcome assessor, and Demir[36] on completeness of the outcome data, whereas the other studies lacked information. The fact that a protocol was not available for any of the animal studies is also noteworthy. This leads to unclear risk of reporting bias and poor transparency in general. In the case of Schreiber[42] it was also mentioned that data for some outcome was not shown, which causes a high risk of bias for outcome reporting. We classified Phillips[43] as assessing both prevention and treatment effects, as we considered the pups treated with antileukotriene in normoxic conditions as the prevention group and the pups with hyperoxia as the treatment group. Seven studies had an experimental design, i.e. the animals were exposed to two or more different interventions, whereas in the remaining three studies all animals received the same intervention and were therefore defined as observational.

Only one study reported outcome data following hospital discharge.[50] Kim et al.[46] is the first prospective study of montelukast for very preterm infants. Min Kim[48] was a cohort study with a historical control group. The study did not provide a clear definition of the inclusion and exclusion criteria, which leads to a serious risk of bias in the selection of participants.

Relation to other research

A study from 2019 evaluated incidence trends of neonates born very preterm in 11 high-income countries and reported increased BPD rates in most countries.[51] Main reasons for this trend include the increased survival of extremely preterm infants and active resuscitation at lower gestational age. Additional interventions are needed to prevent and treat this condition. Of note, montelukast is already being used as a drug in infants with BPD.[52] Interestingly, in this leaflet released/published by American Thoracic Society, montelukast is only listed as an anti-inflammatory medicine for children with BPD.

The administration of off-label drugs in neonates are a universal problem. This forces the neonatologist to rely mostly on clinical experience, expert consensus and data extrapolation from patients other than neonates when deciding upon drug choice and dosage.[53] This supports the need for additional high quality research on this topic. We identified one ongoing observational study that aims to explore the effects of montelukast on very low birth weight infants with BPD.[35] The planned sample size, 200 infants, is considerably larger than the clinical studies performed so far and might allow to better explore potential harms of

Table 7 Outcomes of the clinical studies

	Cheng 2014	Kim 2015	Min Kim 2009	Panjwani 2016	Rupprecht 2014
All-cause mortality (initial hospitalization)	0/6 Mortality seems not to be a prespecified outcome in this study, however no infants died	Not reported	INTERVENTION: 0/15 CONTROL: not reported	3/13 (2 had an antenatal history of oligohydramnios)	INTERVENTION 1/11 CONTROL 7/11
BPD definition (NIH/Jobe / Walsh/unclear)	Treatment study	Jobe INTERVENTION: mild 17/30; mod/severe 13/30 CONTROL: mild 17/36, mod/severe 19/36	NIH INTERVENTION: mild 4/15 moderate 5/15 severe 6/15 CONTROL: mild 5/15 moderate 3/15 severe 7/15	Treatment study	Treatment study
Harms	Not reported	INTERVENTION / CONTROL Infection: 8/3 Gastrointestinal disorders: 5/1 Blood and lymphatic system disorders: 2/1 Cardiac disorders: 1/0 General disorders and administration site conditions: 2/1 Hepatobiliary disorders: 1/0 Pregnancy, puerperium and perinatal conditions: 1/0 Renal and urinary disorders: 2/0 Respiratory, thoracic and mediastinal disorders: 1/1 Vascular disorders: 1/0 Investigations: 4/6	INTERVENTION/ CONTROL Fever: 0/0 Diarrhea: 1/2 Cough: 0/0 Dermatatis: 0/0 Hypersensitivity reactions: 0/0 Vomiting symptoms: 0/0 t	" No obvious side effects were noted"	No drugs-associated adverse events were identified; unclear about other adverse events
Hospital stay	ranging 98–138 days				
All-cause neonatal mortality	0	Not reported	Not reported	Not reported	Treatment study, no info about the time of drug administration
Respiratory support (duration, days)	ranging 7–77 days	Not reported	Not reported	mean ventilation days 41.4 (range 7–69)	INTERVENTION: mechanical ventilation time: mean 41.2 SD 25.3 days CONTROL: mechanical ventilation: 103.7 SD 90.6 days
Need for mechanical ventilation	Not reported	INTERVENTION: 7/37 at 2 weeks CONTROL: 7/40 at two weeks	INTERVENTION: before intervention: 11/15 after 2 weeks of montelukast 7 CONTROL: before intervention: 11; after 2 weeks of montelukast 8	Not reported	Not reported
Major neurodevelop-mental disability	Mental developmental index at two years old: ranging 76–108 PDI at two years old: ranging 96–114				
Retinopathy of prematurity	1	Not reported	Not reported	8	Not reported

None of the included studies reported on the following outcomes: FiO_2 (duration, days), pulmonary function testing at school age

antileukotrienes administration. However, a randomized design would be preferable to assess the efficacy.

Strengths and weaknesses of our review

This is the first systematic review that explores the evidence base of antileukotrienes in very preterm infants in both clinical and animal studies. The review has several strengths. We conducted a comprehensive search with no date or language restrictions. We had studies translated from Mandarin[38] and Korean to English.[48] Further, all the potentially eligible titles and abstracts were screened independently by two authors, as were data extraction and the assessment of risk of bias. We used the most recent and validated tools to assess risk of bias in trials, non-randomized studies and animal studies.

Limitations include our arbitrary definition of neonate animals, i.e. up to 10 days of life. As the definition of a newborn infant (up to 28 days of life) is not based on a specific developmental phase or level of maturation it is not possible to identify a corresponding age in animal models. Further, we did not find any metaanalyses feasible. To retrieve additional information we contacted the authors of two conference abstracts and of the registered protocol we identified in our searches, however, we did not receive any response. Therefore, we could not include these studies and this restriction, though outside of our control, is a potential source of bias.

Implications for research and practice

Refining the existing models to recapitulate the pathology at play in the infants is an urgent matter in order to better evaluate new interventions for BPD.[54] Most animal experiments are carried out to gather information about health in humans and aim to investigate new interventions that are intended for future use in humans. Differences in outcomes in animals and humans are partly due to fundamental biological differences. However, other factors such as for instance design, conduct and reporting play an equally important role.[55] Future animal studies should be designed with higher quality and aim to minimize potential sources of bias, as described in the SYRCLE tool.[28] The registration of the protocols of animal studies in free databases such as https://preclinicaltrials.eu/ should become a standard practice and become a formal requirement placed by journals to publish such studies, as is already commonly done for the clinical studies. Similarly, an appropriate randomization should be performed to ensure that animals in each group are in the same housing conditions (e.g. temperature, humidity, light, noise, odors) and to avoid that researchers subjectively select which animals and samples to be used for outcome assessment. Finally, animal studies should clearly report how many animals were used in each step of the experiment, from inclusion to reporting of all outcomes, so that attrition bias can be assessed. As all the animal studies included in this review failed to address these key components in conducting and reporting, the translational value is extremely limited.

Seven of the ten animal studies used an antileukotriene other than montelukast. We speculate that, unless justified by species or pharmacokinetics characteristics, in future animal studies only montelukast should be administered, as only this drug has been used in all clinical studies so far, including the large ongoing study. When choosing outcomes, the focus should be on those with clinical relevance, such as mortality, improved respiratory function and harms.

Future clinical studies should preferably be designed as large, high quality RCTs.[56] New trials are necessary as the harms are not negligible. The findings of the ongoing study[35] with a planned sample size of 200 infants are not available yet. Multicenter RCTs would be an option in order to reach a sufficient sample size. Just as for animal studies, the focus should be on clinically relevant outcomes.

Conclusions

Based on the available evidence, no reliable conclusions about the clinical relevance of antileukotriene administration to very preterm infants can be drawn. Large randomized trials that focus on outcomes relevant to patients and their families, including long-term outcomes, are needed. Animal studies should prioritize montelukast over other antileukotrienes and minimize risks of bias.

Appendix

Abbreviations

BPD: Bronchopulmonary dysplasia; CI: Confidence interval; IL: Interleukin; IQ: Intelligence quotient; LTRA: Antileukotriene receptor antagonist; MD: Mean difference; NICU: Neonatal intensive care unit; NRSI: Non-randomized study of intervention; RR: Risk ratio; SD: Standard deviation; GRADE: Grading of Recommendations Assessment, Development and Evaluation.

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Authors' contributions

MJ screened studies for inclusion, performed data extraction and drafted the manuscript. FB screened studies for inclusion, performed data extraction and revised the manuscript. GS participated in the design of the study, screened studies for inclusion and performed data extraction. KJ provided methodological support and revised the manuscript. MB conceived of the study, participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data are available by accessing the published studies listed in Tables 1 and 2.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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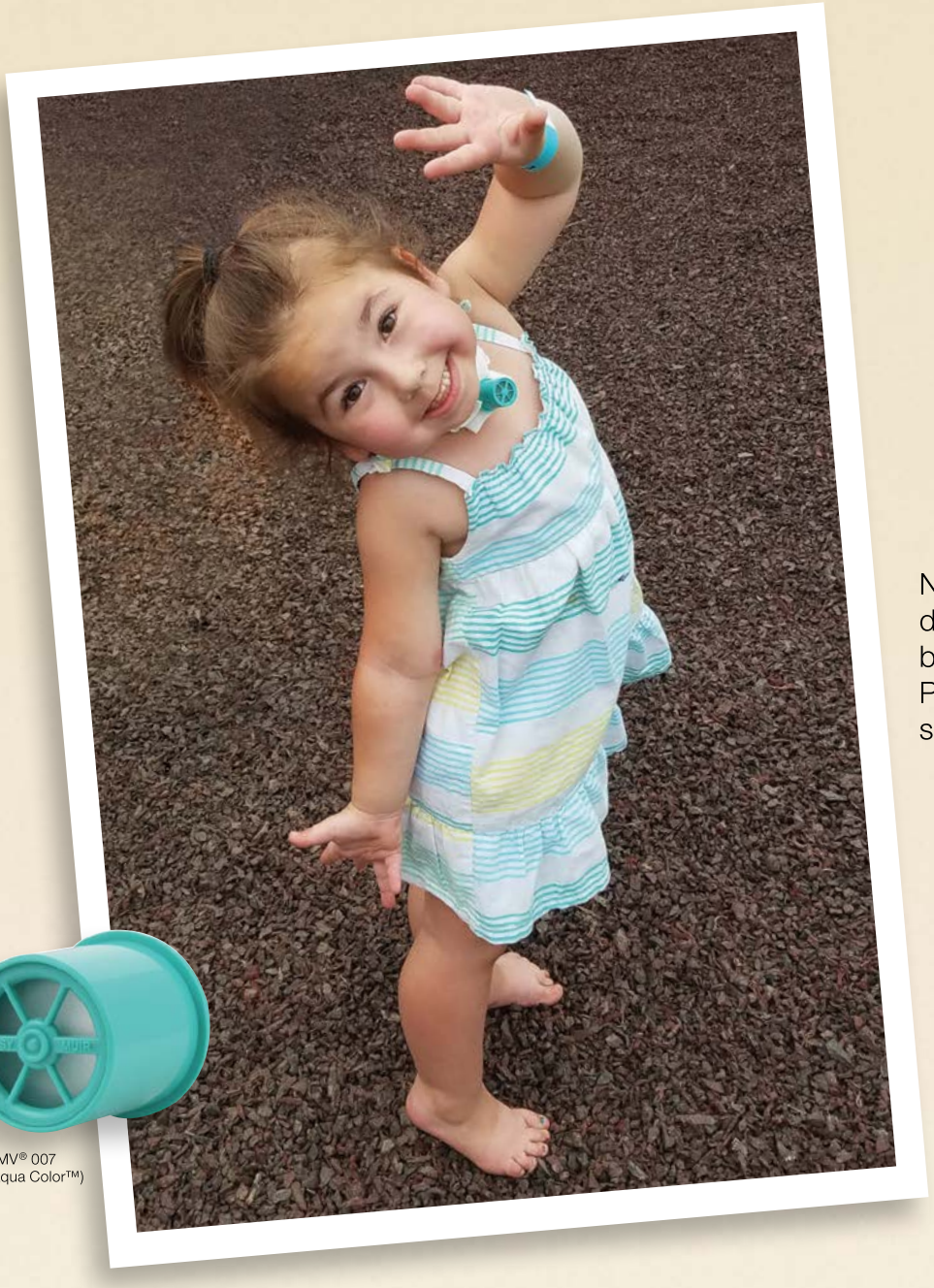

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