In this review:

- Early IV antibiotics reduces mortality in sepsis
- DOT for MDR TB lowers mortality rate
- Benralizumab: oral glucocorticoid-sparing therapy in severe asthma
- Home NIV plus O2 beneficial in COPD + persistent hypercapnia
- MK-7264 for chronic cough
- Optimising antibiotics for adult outpatients with CAP
- Macitentan in inoperable chronic thromboembolic pulmonary hypertension
- Zephyr endobronchial valves: beneficial in both homogenous
- ...and heterogeneous emphysema
- Omalizumab may improve long-term outcomes in adolescent asthma

Abbreviations used in this review:

- 6MWD = 6-minute walk distance
- CAP = community-acquired pneumonia
- COPD = chronic obstructive pulmonary disease
- DOT = directly observed therapy
- ED = emergency department
- IV = intravenous
- MDR = multidrug-resistant
- NIV = noninvasive ventilation
- TB = tuberculosis

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Welcome to this review of the American Thoracic Society (ATS) 2017 International Conference.

ATS 2017 marked the 113th year of the conference, making it the longest running, large-scale conference in the world offering groundbreaking research in pulmonary, critical care, and sleep medicine. Clinicians, researchers, and related health care professionals from more than 90 countries worldwide attended ATS 2017 to connect with world-renowned leaders and colleagues across disciplines on the latest scientific research and findings in medical science and thoracic medicine.

Peter Wark is a senior staff specialist in Respiratory and Sleep Medicine at John Hunter Hospital, Newcastle and a Conjoint Professor with the University of Newcastle, New South Wales. He attended the conference and independently selected and reviewed the presentations included in this review.

I hope you enjoy this review and I look forward to your feedback.

Kind Regards,

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Time to treatment and mortality during mandated emergency care for sepsis

Presenter: Christopher W. Seymour, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Summary: In 2013, New York began requiring hospitals to follow protocols for the early identification and treatment of sepsis. However, considerable controversy exists as to how rapidly to treat patients with sepsis and septic shock. These researchers evaluated cases of sepsis and septic shock reported to the New York State Department of Health from 1 April 2014 to 30 June 2016. Patients had a sepsis protocol initiated within 6 hours after arrival in the emergency department and had all items in a 3-hour bundle of care for patients with sepsis (i.e., blood cultures, broad-spectrum antibiotic agents, and lactate measurement) completed within 12 hours.

Comment: The early use of IV antibiotics in sepsis has been an important addition to guideline recommendations in Australia. A similar concern about delayed treatment of sepsis has also existed in the USA. This study was presented at the ATS by Christopher Seymour of the University of Pittsburgh and published simultaneously in the New England Journal of Medicine. The investigators demonstrated that the earlier use of antibiotics, but not intravenous fluids, was associated with lower in-hospital death rates among patients with suspected sepsis treated in New York state emergency departments (EDs) following the adoption of statewide mandated guidelines. These were implemented in 2015 following the death of a 12-year-old boy from undiagnosed sepsis in a hospital ED.

The study supports the association between time to treatment and outcome among patients with sepsis treated in EDs under the statewide initiative, with each 1-hour delay in correctly administering antibiotics associated with a 4% increase in the odds of death. The primary outcome was in-hospital mortality, and the primary exposure was the time to completion of the 3-hour bundle, which included measurement of lactate, prompt blood culture followed by administration of broad spectrum antibiotic agents, and lactate measurement completed within 12 hours.

Among 49,331 patients treated at 149 hospitals, 40,696 (82.5%) were treated according to protocol within 3 hours. The median time to completion of the 3-hour bundle was 1.30 hours (IQR 0.65-2.35) and the median time to administration of antibiotics was 0.95 hours (IQR 0.35-1.95). The median time to completion of the fluid bolus was 2.56 hours (IQR 1.33-4.20).

Among patients who had the 3-hour bundle completed within 12 hours:

- A longer time to bundle completion was associated with higher risk-adjusted in-hospital mortality (OR 1.04 per hour; 95% CI, 1.02-1.06; p<0.001)
- A longer time to antibiotic administration was also associated with higher adjusted in-hospital mortality (OR 1.04 per hour; 95% CI, 1.03-1.06; p<0.001)
- A longer time to bolus IV fluids was not associated with a statistically significant increase in mortality (OR 1.01; 95% CI, 0.99-1.02; p=0.21)

Interestingly, despite these changes being mandated by law, there were still variations in protocol completion times from hospital to hospital.

Factors associated with mortality among patients with multidrug-resistant tuberculosis – United States, 1993-2013

Presenter: Jorge Salinas, Centers for Disease Control and Prevention, Atlanta, GA, USA

Summary: This study analysed surveillance data from 3,434 multidrug-resistant tuberculosis (MDR TB) patients treated in the USA from 1993 through 2013. The researchers examined the association of treatment administration mode (directly observed therapy [DOT] versus self-administered therapy) with all-cause mortality during TB treatment, accounting for age (per 5-year increments), sex, race/ethnicity, HIV infection, previous TB disease, site of disease (i.e., pulmonary versus extrapulmonary), and additional drug resistance (i.e., resistance to at least one fluorquinolone or a second-line injectable drug). A total of 709 patients died during TB treatment. Of the entire study cohort, 34% had HIV infection, 18% had a previous diagnosis of TB disease, 17% had additional drug resistance, and 88% were of either Asian or Hispanic race/ethnicity.

While DOT is recommended to treat all forms of TB, this data confirmed its effectiveness even in patients with MDR TB. Half the patients (50%) were Asian and a third (33%) were Hispanic. Older age (aHR 1.15; 95% CI, 1.11-1.20) and reported HIV infection (aHR 7.11; 95% CI, 5.46-9.24) were risk factors for all-cause mortality irrespective of patient’s origin or period of treatment. Receiving DOT (aHR 0.23; 95% CI, 0.19-0.28) was protective in all stratified models.

Reference: Am J Respir Crit Care Med. 2017;195:A1186

Abstract

Oral glucocorticoid-sparing effect of benralizumab in severe asthma

Presenter: Parameswaran Nair, McMaster University and St. Joseph’s Healthcare, Hamilton, ON, Canada

Summary/Comment: This study set out to determine whether benralizumab, a monoclonal antibody directed against the alpha subunit of the interleukin-5 receptor would significantly reduce asthma exacerbations, as well as act as an effective oral glucocorticoid–sparing therapy in patients relying on oral glucocorticoids to manage severe asthma associated with eosinophilia.

This was a 28-week randomised, controlled trial, investigating benralizumab (at a dose of 30 mg administered subcutaneously either every 4 weeks or every 8 weeks [with the first 3 doses administered every 4 weeks]) versus placebo in the reduction in the oral glucocorticoid dose while asthma control was maintained in adult patients with severe asthma. The primary end point was the percentage change in the oral glucocorticoid dose from baseline to week 28. Participants were eligible if they had a blood eosinophil count ≥150 cells/mm³ and had asthma that had been treated with medium-dose to high-dose inhaled glucocorticoid and long-acting β2 agonist (LABA) therapy for ≥12 months before enrolment and treated with high-dose inhaled glucocorticoid and LABA therapy for ≥6 months before enrolment. Patients had been receiving oral glucocorticoid therapy for ≥6 continuous months directly before enrolment (equivalent to a prednisolone or prednisone dose of 7.5 to 40.0 mg/day).

There were 220 patients randomised and who started receiving benralizumab or placebo. The two benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75%, as compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group (p<0.001 for both comparisons). The odds of a reduction in the oral glucocorticoid dose was more than 4 times higher with benralizumab than with placebo.

Among the secondary outcomes, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than the rate with placebo (marginal rate, 0.83 vs 1.83; p=0.003), and benralizumab administered every 8 weeks resulted in an annual exacerbation rate that was 70% lower than the rate with placebo (marginal rate, 0.54 vs 1.83; p<0.001). At 28 weeks, there was no significant effect of either benralizumab regimen on FEV₁, as compared with placebo.

Benralizumab allowed this group with oral glucocorticoid-dependent asthma to reduce their oral corticosteroids significantly, while still reducing the risk of exacerbations. It is noteworthy that the entry criteria for this group required a lower blood eosinophil count than current Australian PBS requirements, in acknowledgment of the suppressive effect that oral corticosteroids themselves will have.


Abstract

Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation

Presenter: Patrick B. Murphy, Guy’s and St Thomas’ NHS Foundation Trust, London, UK

Summary: The data presented from this study indicate that the addition of home noninvasive ventilation (NIV) to home oxygen therapy may improve outcomes in patients with severe chronic obstructive pulmonary disease (COPD) and persistent hypercapnia following hospital admission.

Comment: The outcomes after exacerbations of COPD that are complicated by acute hypercapnic respiratory failure and require treatment with NIV are known to be poor and are associated with a high risk for readmission and death. This UK multicentre study set out to investigate the effect of home NIV plus oxygen on time to readmission or death in patients with persistent hypercapnia within a month of their acute COPD exacerbation.

This was a randomised clinical trial of patients who were seen within a month (2–4 weeks) of their acute exacerbation of COPD (with and without) persistent hypercapnia (PaCO₂ >53 mm Hg) after resolution of respiratory acidemia. They were recruited from 13 UK centres between 2010 and 2015. Exclusion criteria included obesity (body mass index [BMI] >35), due to concern they might have undiagnosed OSA, diagnosed obstructive sleep apnoea syndrome, or other causes of respiratory failure. Of 2,021 patients screened, 124 were eligible.

Fifty-nine patients were randomised to home oxygen alone (median oxygen flow rate, 1.0 L/min) and 57 patients to home oxygen plus home NIV (median oxygen flow rate, 1.0 L/min). The median home ventilator settings were an inspiratory positive airway pressure of 24 cm H₂O, an expiratory positive airway pressure of 4 cm H₂O, and a backup rate of 14 breaths/minute. The primary outcome was time to readmission or death within 12 months and was adjusted for the number of previous COPD admissions, previous use of long-term oxygen, age, and BMI.

Sixty-four patients (28 received home oxygen alone and 36 home oxygen plus home NIV) completed the 12-month study period. The median time to readmission or death was 4.3 months in the home oxygen plus home NIV group vs 1.4 months in the home oxygen alone group (aHR 0.49; 95% CI, 0.31-0.77; p=0.002). The 12-month risk of readmission or death was 63.4% in the home oxygen plus home NIV group vs 80.4% in the home oxygen alone group, yielding an absolute risk reduction of 17.0% (95% CI, 0.1%-34.0%). At 12 months, 16 patients had died in the home oxygen plus home NIV group vs 19 in the home oxygen alone group.

The investigators have shown that among patients with persistent hypercapnia following an acute exacerbation of COPD, adding home NIV to home oxygen therapy prolonged the time to readmission or death within 12 months. This trial answers a very important question in the management of end-stage COPD and shows a clear benefit to the patients who received NIV and oxygen and who met these criteria. The clinical need for these patients is high and this study demonstrates a clear way forward, identifying those who will benefit and demonstrating clinically important outcomes. It is a treatment that needs to be considered for adoption in this group.

Reference: JAMA. 2017;317(2):2177-86

Abstract
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**Clinical predictors of antibiotic failure in adult outpatients with community-acquired pneumonia**

**Presenter:** J McKinnell, UCLA, Los Angeles, CA, USA

**Summary:** Antibiotic failure for community-acquired pneumonia (CAP) is associated with significant morbidity and mortality, as well as high medical costs. This retrospective analysis of outpatient CAP data from MarketScan Commercial & Medicare Supplemental Databases covered the period from 2011 through 2015 and included patients aged ≥18 years who had received antibiotic therapy following an outpatient visit for CAP.

**Comment:** The researchers examined databases containing records for 251,947 adult outpatients who were treated between 2011 and 2015 with a single class of antibiotics (beta-lactam, macrolide, tetracycline, or fluoroquinolone) following a visit to their physician for treatment for CAP. The scientists defined treatment failure as either the need to refill antibiotic prescriptions, antibiotic switch, ED visit or hospitalisation within 30 days of receipt of the initial antibiotic prescription.

The total antibiotic failure rate was 22.1%, while patients with certain characteristics – such as older age, or having certain other diseases in addition to pneumonia – had higher rates of drug failure. After adjusting for patient characteristics, the failure rates by class of antibiotic were: beta-lactams (25.7%), macrolides (22.9%), tetracyclines (22.5%), and fluoroquinolones (20.8%).

Patients over the age of 65 were nearly twice as likely to be hospitalised compared to younger patients when the analysis was risk-adjusted and nearly 3 times more likely in unadjusted analysis. Elderly patients are more vulnerable and should be treated more carefully, particularly with more aggressive treatment.

There were substantial regional variations in treatment outcomes, which are not addressed in a specific way in the current CAP guidelines. In addition, the study showed that thousands of patients who suffer from other conditions – such as COPD, cancer or diabetes – were not treated with combination antibiotic therapy or respiratory fluoroquinolone, as the guidelines recommend.

The study certainly demonstrated the shortcomings for outpatient treatment of CAP. However, there are major differences between the US and Australian guidelines, which may limit the relevance of these findings to Australia. Nevertheless, it did clearly show that in all patients with pneumonia, an assessment of comorbidities and clinical severity needs to be made and the guidelines should be applied, as opposed to practitioners prescribing agents that are not currently recommended.

**Reference:** Am J Respir Crit Care Med. 2017;195:A6244

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**Efficacy and safety of macitentan for inoperable chronic thromboembolic pulmonary hypertension: results from the randomized controlled MERIT study**

**Presenter:** Hossein Ardeshir Ghorani, Universities of Giessen and Marburg Lung Center, Giessen, Germany

**Summary:** The MERIT study recruited patients with primary inoperable chronic thromboembolic pulmonary hypertension in WHO functional class (FC) II–IV with a pulmonary vascular resistance (PVR) ≥400 dyne·sec/cm² and 6-minute walk distance (6MWD) ≤150 m and ≤450 m. Treatment with phosphodiesterase type 5 inhibitors (PDE5is) or oral/inhaled prostanooids could be administered to patients in WHO FC III–IV, but not to those in WHO FC II. Patients were randomly assigned to placebo (n=40) or macitentan 10 mg (n=40) once daily for 24 weeks.

**Comment:** Chronic thromboembolic pulmonary hypertension, while rare, is an important and increasingly recognised cause of pulmonary hypertension leading to chronic severe breathlessness and right heart failure. The authors presented the results of a study showing that macitentan, an oral endothelin receptor antagonist (Actelion), can lead to significant improvements in pulmonary vascular resistance and exercise capacity.

Of the participants who were receiving therapy for pulmonary hypertension at baseline, 96% were receiving PDE5is and 24% were receiving oral or inhaled prostanooids. For the primary end point of pulmonary vascular resistance at 16 weeks, expressed as a percentage of baseline, macitentan was associated with a significant 16% reduction compared with placebo (p=0.04). There was no difference between people who continued their baseline therapy and those who did not, or between the different types of pulmonary hypertension treatment. Mean improvement in 6MWD from baseline to 24 weeks – the main secondary end point and an indication of overall exercise capacity – was significantly better in the macitentan group than in the placebo group (53 vs 1 m; p=0.03).

Chronic thromboembolic pulmonary hypertension is an important problem and not all patients are candidates for pulmonary thromboendarterectomy because of the location of the thrombi or other comorbidities. Only one other agent, riociguat, has been shown to improve outcomes in this setting. Endothelin receptor antagonists should be considered as a treatment option in these patients.

**Reference:** Am J Respir Crit Care Med. 2017;195:A6740

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**A multicenter, prospective, randomized, controlled trial of endobronchial valve treatment vs standard of care in heterogeneous emphysema (TRANSFORM)**

**Presenter:** Samuel V. Kemp, Royal Brompton and Harefield NHS Foundation Trust, London, UK

**Summary:** TRANSFORM enrolled patients with hyperinflation (FEV, ≤45% predicted, residual volume [RV] ≥810% predicted), decreased exercise capacity (6MWD of ≤450m) and severe heterogeneous emphysema, confirmed by quantitative high-resolution computed tomography (HRCT) and scintigraphy.

**Comment:** The TRANSFORM study, a multicentre, prospective, randomised controlled trial, evaluated 97 patients with heterogeneous (more focally-distributed) emphysema at 17 centres in 6 countries. Patients were randomised 2:1 to Zephyr® valve treatment versus standard of care. The authors concluded that Zephyr® valve treatment in heterogeneous emphysema patients without collateral ventilation confers clinically and statistically significant sustained benefits, with improvements in lung function, exercise capacity and quality of life.

Six-month follow-up data from TRANSFORM revealed:
- Average increase FEV1: 29.3%
- Average increase 6MWT: 78.7 m
- Average increase in the St. George’s Respiratory Questionnaire (SGRQ) score: 6.5 points

The investigators used the Chartis Pulmonary Assessment System to ensure there was no collateral ventilation in the targeted lobes.

**Reference:** Am J Respir Crit Care Med. 2017;195:A6740

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**MK-7264, a P2X3 receptor antagonist, reduces cough frequency in patients with refractory chronic cough: results from a randomized, controlled, phase 2b clinical trial**

**Presenter:** Jacky Smith, Manchester, UK

**Summary:** Effective treatments for chronic cough are a significant unmet clinical need. MK-7264, an antagonist of the purinergic receptor, P2X3, has previously demonstrated efficacy at a high dose in a study of patients with refractory chronic cough (see Abdulqawi R, et al. J accent 2015;385:1198-205). This 12-week, phase 2b clinical trial evaluated the safety, efficacy, and therapeutic dose range of MK-7264 for the treatment of chronic cough.

**Comment:** In this phase 2 study, Smith et al. compared MK-7264 with placebo in patients with refractory chronic cough from 46 sites in the United Kingdom and the United States. Of the 253 study participants, 64 were randomly assigned to a twice-daily 7.5 mg dose of MK-7264 for 12 weeks, 63 were assigned to a twice-daily 20 mg dose, 63 were assigned to a twice-daily 50 mg dose, and 63 were assigned to placebo. Average age in the study cohort was 60 years, and 76% of the patients were women. The investigators assessed cough frequency with a VitaloJAK digital recording device from Vitalograph, and cough severity with a visual analogue scale (0–100 mm VAS).

Control of cough improved with the higher dose, although the number of patients who reported dysgeusia – a taste disorder in which a foul, salty, rancid, or metallic taste persists in the mouth – increased as the dose increased. In fact, six patients in the 50 mg group discontinued the drug because of this.

Despite the problems of taste, this is the second trial to show that this agent is effective in controlling chronic cough. While cough is not a life-threatening problem, it does cause significant chronic morbidity and is an important reason for referral to respiratory physicians. While dose could not be adjusted in the trial, this could be the case in real life, where patients could balance this against control of cough. This agent remains an important potential treatment for chronic cough.

**Reference:** Am J Respir Crit Care Med. 2017;195:A7608
Endobronchial valve treatment in homogeneous emphysema: 6-month follow-up in the IMPACT randomized controlled trial

Presenter: Dirk-Jan Slebos, University of Groningen, University Medical Center Groningen, The Netherlands

Summary/Comment: The IMPACT study enrolled 93 patients with severe homogeneous (more diffusely-distributed) emphysema and randomised them 1:1 to Zephyr® valve treatment versus medical management. Consistent with the previously published 3-month data, the improvements remained statistically and clinically significant at 6 months with Zephyr valve-treated patients experiencing improvements over control for FEV₁ of 16.3% (p<0.001), an increase in 6MWD of 28.3m (p=0.016), and an improvement in quality of life based on a decrease in the SGRQ score of –7.5 points (p<0.001). Six-month follow-up data from IMPACT:

- Average increase FEV₁: 16.3%
- Average increase 6MWT: 28.3m
- Average improvement SGRQ: 7.5 points

The most common side effect of the Zephyr valves in both studies was pneumothorax (20–26% in the treated group) and COPD exacerbations (11–28% vs 6–18% in the control group) in the immediate post-procedure period. Both were addressed with standard medical management.

The results from TRANSFORM and IMPACT now support the previously 2 reported trials (the STELVIO and Beil Excr-HIFTr trials) that demonstrate substantial improvements in quality of life, lung function and exercise tolerance in individuals with severe emphysema and dynamic hyperinflation. For this group of patients, treatment with endoscopic pulmonary valves needs to be considered as a viable treatment option, although they are not without their risks. For Australian patients where access is limited to those with private health insurance, the case seems to be strong for this to be considered and reimbursed.

Reference: Am J Respir Crit Care Med. 2017;195:A5719
Abstract